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THE MEDICAL CLINICS

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Volume 10 No. 3

MEDICAL CLINIC OF ARCH H. LOGAN

REPORTED BY PHILIP W. BROWN

For our clinic today we have a group of cases which illustrate some of the problems involved in the diagnosis of abdominal diseases. Especially in the diagnosis of tumors of the bowel and the various forms of diarrhea there is much uncertainty in spite of refinements of technic. Estimation of the gastric acids, roentgenographic examination of the intestinal tract, proctoscopy, and examinations of the stools, both cultured and microscopic, are all or in part frequently necessary for the diagnosis. One of the most valuable considerations is a carefully taken history. An efficient laboratory armamentarium too often tempts us to resort to "tests" when the history itself holds the clue to the problem.

As we review the following cases I wish to emphasize a few special points that may be obtained by careful physical examination. Inspection is sometimes of much aid to us. By firm but gentle palpation one may outline almost the entire course of the colon. Deep palpation above Poupart's ligament and along the lumbar spine may disclose the presence of enlarged lymph nodes. In abdominal diseases and even in rectal lesions there is no superficial inguinal adenopathy; it is only when a lesion involves the anus that there is any enlargement of the inguinal lymph nodes. Ballottement is sometimes valuable in revealing evidence of ascites or a tumor. A proper physical examination of the abdomen is more than a perfunctory poke or

punch; it can be developed into as much of an art as the examination of the chest.

A final point to remember is that rectal examination should be a routine measure. One should learn to distinguish the bleeding and discharge of hemorrhoids, fissure and fistula, and to examine the rectum digitally higher than the anal canal. Operation for hemorrhoids should never be performed until cancer has been excluded, since in one-fifth of the cases of rectal cancer seen at the Clinic, operation for hemorrhoids was performed elsewhere a few months previously. Examination of the rectal shelf will often clearly establish a diagnosis and obviate a needless operation.

Only the essentials of the history and of the examinations will be given in the following cases.

Case 1.—This patient, a male aged fifty-eight, gives a history dating back eighteen years when he began to pass blood and mucus from the rectum. At times the bowels have been loose, but there has been no severe diarrhea. He has had much treatment by mouth without benefit. Three months prior to admission to the Clinic he had had a severe hemorrhage. Hemorrhoidectomy was performed. Since then he has lost much blood and there have been frequent calls to stool when he would pass only bloody material. There has been difficulty in urination for the last few months.

At this time he is weak; he has lost 30 pounds in the last three months. The general physical examination is quite negative, otherwise, for a man of his age. Digital examination of the rectum is negative. The urine shows a moderate amount of pus. The hemoglobin is 68 per cent; erythrocytes number 4,000,000, and leukocytes 8,400. The blood Wassermann reaction is negative. On test of renal function there is a return of 55 per cent in two hours. On proctoscopic examination a fixed mass is seen in the rectosigmoid which is practically obstructing the lumen of the bowel.

Comment.—This case is very interesting because the patient has suffered from recurrent ulceration of the rectosigmoid for eighteen years, which in the last few months has taken on new features, particularly the marked bleeding and loss of weight. A further point to emphasize is that only three months ago he was subjected to hemorrhoidectomy. An operation to explore the mass is now advised. In a series of 560 cases of chronic ulcerative colitis, malignant tumors of the colon or rectum have occurred in less than 1 per cent. I think that this man had an

ulcerative lesion which belongs in the ulcerative colitis group, but at this time there is likely a malignant process.

Operation later revealed a carcinoma which was so fixed that resection was impossible. Palliative colostomy was performed.

Case 2.—This patient is a man aged thirty-one. Ten years ago he began to have pain in the lower right quadrant of the abdomen. No severe attacks occurred, but there was a more or less dull ache all the time. During two years, while in the army, he had very little trouble. His symptoms recurred and persisted until ten months ago, when he underwent an operation to explore the appendix. At operation an indeterminate mat of adhesions was found, and appendectomy was performed. He recovered satisfactorily and felt well until three weeks ago, when a tender mass was felt in the lower middle portion of the abdomen. He began to lose weight. Increasing difficulty in obtaining bowel movements was noted.

On physical examination we find a fairly healthy appearing man. In the lower right and middle portions of the abdomen a smooth tender mass is easily felt on bimanual examination. On repeated counts the leukocytes average 11,000. The blood Wassermann test is negative. Physical examination of the chest, as well as roentgenograms, is negative. With the barium enema, a lesion of the cecum is found, which seems adherent to the sigmoid. On repeated tests the stool has been negative for ova, parasites, and bacillus of tuberculosis.

The diagnosis in this case is probably inflammatory lesion of the ileocecal coil which has become adherent to the sigmoid. Tuberculoma must be kept in mind, although it is more likely to be a nonspecific granuloma following operation. After a few days' rest in bed, liquid diet, and ice-bags over the mass he will undergo operation.

Comment.—It developed that the patient had an inflamed Meckel's diverticulum which had adhered to the sigmoid and was the source of the extensive adhesions. After a rather stormy convalescence he completely recovered.

Case 3.—This patient, aged fifty-five, first consulted us two years ago, at which time he was found to have tabes dorsalis. In his family history it is of interest to note that one brother, one sister, and two grandparents died from carcinoma.

He now returns for further antisyphilitic treatment and in the course of his reëxaminations he gives us new information. About four months ago he noted a movable mass in the middle of the abdomen. He had always been constipated, but this became worse. Also there was so much mucus passing from the rectum that it was necessary to wear a pad.

On physical examination the patient revealed all the classical signs of tabes. There is a movable, painless mass, palpable in the right side of the abdomen. On rectal examination, a small, movable growth is felt on the anterior wall. The roentgenogram of the colon reveals a lesion in the cecum.

This man presents the problem of a lesion of the cecum, which is probably carcinoma, with another lesion in the rectum, also malignant. It is possible that the small rectal carcinoma is an implantation of carcinoma cells from the cecal tumor on a rectal polyp. This observation is comparable to the occurrence of a metastatic mass in the culdesac in cases of carcinoma of the stomach. The coexistent tabes increases the operative risk, and yet operation should be undertaken. First, the rectal lesion will be treated temporarily with radium and then the cecal tumor will be explored.

Comment.—Operation revealed an adenocarcinoma of the cecum, which was resected. Convalescence was uneventful. At a later date the residue at the site of the rectal lesion was removed without incident.

Case 4.—This patient is a woman aged fifty-five. Her illness began with the extraction of teeth six weeks prior to her first admission to the Clinic. After the extraction she began to have abdominal distress and diarrhea, which did not respond to ordinary treatment. A week before this first admission there had been one large and two small hemorrhages of bright red blood from the bowel. Since then she has had a constant dull pain in the lower right quadrant of the abdomen. At that time she was weak and pale. The hemoglobin was 47 per cent; the erythrocytes numbered 3,560,000, and the leukocytes 10,900. The urine was normal and the blood Wassermann reaction negative. Roentgenologic studies of the stomach and colon were negative. The proctoscopic examination showed a normal mucosa. In the stool *Endamœba histolytica* was identified. She was given a course of 6 grains of emetin hydrochlorid hypodermically and there was prompt symptomatic response. She returned home to continue the anti-amebic treatment.

On her return she is a different woman; the bowels are regular; she has regained her weight, and the blood count is normal. Her chief concern is the incontinent anal sphincter resulting from a difficult labor years ago. The barium enema of the colon now shows a lesion of the cecum, even after a course of belladonna. Her general condition is satisfactory and the question is whether a residue of amebic colitis could produce this syndrome or whether, in a woman of her age, there is not a possibility of an early malignant lesion. It seems safer to advise operation to explore the cecum, and later repair the anal sphincter.

Comment.—Operation revealed a chronically inflamed appendix, buried in a mass of adhesions. The cecum and ascending colon showed evidence of chronic colitis. Appendectomy was

performed and convalescence was uneventful. Still later the anal sphincter was repaired.

Case 5.—This patient, a woman aged twenty-four, was always well until the spring of 1923, when she was seized with acute pain in the right side of the abdomen, with nausea and vomiting. This attack subsided. Later appendectomy was performed and the surgeon informed her that everything else was normal. She was quite well until March, 1925, when she became weak and complained of night sweats and afternoon fever. In April a sudden feeling of weakness was followed by the passage of bright bloody stools. Transfusion was carried out as an emergency. A tumor was felt in the cecal region. Since then the patient has continued to be weak and to complain of a dull ache in the right side of the abdomen; slight fever has been present, but no further hemorrhage has occurred.

Examination shows that the patient is a pale, thin, young woman. The chart shows an afternoon rise in temperature daily. The hemoglobin is 35 per cent; the erythrocytes number 3,220,000, and the leukocytes 5,500. The blood Wassermann reaction is negative. Roentgenograms of the chest are negative. The barium enema of the colon reveals a filling defect in the cecum and terminal ileum. The mass responsible for it is easily palpable. On bimanual examination it does not seem to be connected with the pelvic organs.

Three diseases are to be especially considered in this case: tuberculoma of the ileocecal coil, nonspecific granuloma, and malignant neoplasm. The patient's age, good health generally since the first serious attack, and the afternoon fever lead us to consider an inflammatory lesion, very possibly tuberculosis. The roentgenogram of the lungs is negative and there are no physical findings of pulmonary tuberculosis. If this tumor is tuberculous, it is one of the infrequent cases of primary tuberculoma of the bowel. Severe hemorrhage from a tuberculoma is very rare, and this one point in the history makes us fear the presence of carcinoma. Operation is advised.

Comment.—Operation revealed an extensive, adherent mass. Specimens were removed and reported to be adenocarcinoma. Ileocolostomy was performed. At a second operation the tumor was resected and convalescence was uneventful.

Case 6.—This man, aged twenty-three, is a native of Austria, and has been a coal miner in the West. Owing to his difficulty with the language, we are unable to elicit a definite history. He is concerned about an old gonorrheal infection and he seems to be below par for no reason in particular. About two years ago he had a cough, and the possibility of pulmonary tuberculosis was considered. He has no digestive disorders and his bowels are regular. His weight is normal. Physical examination has revealed evidence of a quiescent lesion of the upper lobe of the right lung; this was confirmed by roentgenograms. In the lower right side of the abdomen there is felt an

oval, movable, painless tumor. The blood count is normal and the blood Wassermann reaction negative.

At the patient's first visit it was noted that the urine was normal. In view of the possibility of a low-lying right kidney the urine was again examined and now found to contain erythrocytes. Cystoscopic examination proved the tumor to be extrarenal.

This morning the report on the roentgenologic examination of the colon was that there is a filling defect in the cecum, a rapid filling and emptying of the ileocecal coil such as occurs with a tuberculous lesion.

The diagnosis of tuberculoma of the cecum is the most likely one in view of the recent developments. We may explain the hematuria on the basis of the inflammatory mass being adherent to the ureter. Our manipulations produced the necessary trauma. This may prove to be a nonspecific granuloma. It is probably not due to actinomycosis as there is no evidence of external sinuses. A syphilitic lesion of this nature is very rare and even more rare with a negative Wassermann reaction. We are not certain whether the pulmonary and intestinal lesions are due to the same infection. Primary tuberculoma of the bowel does occur in a few instances and probably is due to the bovine type of infection. In the case of a patient under forty years of age this clinical picture is most likely to be the result of a tuberculoma of the ileocecal coil. Operation is advised.

Comment.—A hyperplastic tuberculosis of the ileocecal coil was found and resection done.

UNFAMILIAR ASPECTS OF HEMATEMESIS AND MELENA

GEORGE B. EUSTERMAN

Four types of cases illustrating some of the less recognized but frequent causes of hemorrhage from the upper digestive tract are herewith presented. Such cases are illustrative of instances of hemorrhage in ambulant patients seen in the Clinic. In every case of hematemesis or melena, or both, a lesion of the stomach or duodenum should be considered the direct cause until proved not to be. Only about 30 per cent of chronic benign lesions give rise to gross bleeding, and in the majority of malignant lesions the bleeding is occult, gross hemorrhage being manifested in 8 per cent, usually during the late stages of the disease. However, hemorrhage and a history characteristic of ulcer, invariably make the diagnosis of ulcer certain. In a small percentage of cases of peptic ulcer hemorrhage, single or recurrent, may be the only symptom elicited. On the other hand, there is a formidable group of causes extraneous to the stomach itself which may provoke hemorrhage, so that one must not jump too quickly to the conclusion that hematemesis or melena spells an intrinsic gastric or duodenal lesion. In fact, such hemorrhages are usually not due to gastric or duodenal lesions. Some years ago I pointed out the incidences in which, for example, disease of the gallbladder or appendix with associated gastric disturbances may cause hematemesis or melena. The extragastric causes of hematemesis have been more recently reviewed by Balfour. Among these he has emphasized hepatic cirrhosis in its various forms, splenomegaly (splenic anemia, Banti's disease, leukemia, hemolytic jaundice), diseases of the gallbladder, appendix, pancreas and small intestine, disordered conditions of the blood (hemophilia, purpura, cholemia), renal,

cardiac and pulmonary disease, lesions of the nasopharynx and esophagus, external traumatism, and so forth.

REPORT OF CASES

Case 1.—A man, aged sixty, entered the Clinic February 20, 1925 because of indigestion and recent severe melena. He had had dengue fever, tonsillitis, and malaria at the age of twenty-six, and pleurisy following an operation elsewhere for left inguinal hernia in 1923. Tonsillectomy was performed in 1921. His personal habits were good; he denied venereal disease and the family history was essentially unimportant. In the spring of 1923 he complained of a daily dull aching pain in the right epigastrium for about three weeks. About a year later he had a second attack which lasted for about ten days. The pain was well localized, and reached its maximal intensity about four hours after meals and was most marked about midnight. It was relieved by food or alkalis, or by heat applied locally. After biliary drainage (Lyon) several times by a local physician the patient was relieved of all symptoms for about seven months. This was followed by a less severe recurrence, and at the end of a week severe melena occurred with resulting syncope. On the day of the hemorrhage he had driven about fifty golf-balls from the tee, in driving practice. The anemia was marked and he was confined to bed for two weeks. Following this recovery was rapid. Barring constipation he had no other complaints.

The patient was well built and well nourished. The abnormal findings were those of rather marked anemia, mitral regurgitant murmur in a compensated heart, a well-healed operative scar in the left inguinal region, and moderate vascular hypertention. The hemoglobin was 47 per cent (Dare), the erythrocytes numbered 3,000,000 (the color index being 0.7+), and the leukocytes 8,000. The platelet count was reduced, as seems to be the rule after severe hemorrhage, but the coagulation time (Boggs) and bleeding time were within normal limits. Gastric analysis was not carried out owing to the recent hemorrhage. Roentgenoscopic examination of the stomach and duodenum on two occasions showed no abnormality. Roentgenograms of the thoracic organs and colon were essentially negative. A proctoscopic examination revealed some edematous external hemorrhoids and an immobile sigmoid, presumably due to a short mesosigmoid.

In view of the chronic recurring indigestion and severe melena, exploratory operation was advised. This was expected to reveal a lesion in the stomach or duodenum, although cholecystic disease was seriously considered. When the abdomen was opened many pericholecystic adhesions were found, the gallbladder itself having the appearance of that seen in "cholesterosis." However, after removal of the organ multiple papillomas were found inside. There was marked hepatitis in that portion of the liver overlying the gallbladder. The appendix was densely bound down in the pelvis and was removed secondarily. Careful examination of the stomach and duodenum, anteriorly and posteriorly, failed to disclose an ulcer. The patient had an uneventful convalescence and has remained in good health so far.

Comment.—Although this case is not unusual, it is of clinical interest for several reasons. There was a lesion extraneous to the stomach itself, so far as could be determined, not only provoking gastric disturbances, but closely simulating the symptoms characteristic of chronic peptic ulcer. To what extent the regional hepatitis was responsible for the latter is debatable, for bleeding may obtain in the absence of such demonstrable hepatic changes in cholecystic disease. In approximately 5 per cent of patients with chronically diseased gallbladders, having reflex dyspepsia, there is gross gastro-enteric bleeding. In such cases no ulcer is demonstrable at operation and removal of the diseased organ invariably promotes complete cure, with no repetition of the hemorrhages. This group is, of course, exclusive of the 15 to 18 per cent of patients with chronic cholecystic disease in which there is a coexisting chronic ulcer of the stomach or duodenum. The not infrequent combination of an ulcer-like syndrome, lack of free hydrochloric acid in the gastric contents, negative roentgen-ray examination, and even a history of hemorrhage should give rise to a suspicion of cholecystic disease, especially in the absence of cachexia or an abdominal tumor. Finally, the history of unusual exertion or violent exercise, as in this case, is instructive. It has been my experience repeatedly that undue physical activity may precipitate severe hematemesis or melena under certain circumstances, whether the lesion is intrinsic to the stomach or not. Case records in the Clinic are replete with instances of hemorrhage in patients even after years of apparent good health following operation. Such hemorrhages obtain during a strenuous hunting period, while cranking a car in cold weather, while felling a large tree at the summer home by one of sedentary occupation, while driving numerous golf-balls in rapid succession, or as the result of arduous mountain-climbing. Of equal importance in the causation of hemorrhage is an alcoholic debauch. This, in my recent experience, has given rise to a severe hemorrhage in the presence of active, quiescent, or even healed lesions.

Case 2.—A man, aged forty-six, was first examined June 7, 1926. He had had typhoid fever at the age of ten, malaria as a young man, a gonorrheal infection at twenty-one, a simple chancre at the age of thirty-one, and influenza without complications in 1919. He had received mercurial unctions at the time of the primary syphilitic lesion and underwent treatment six years prior to his examination here when a Wassermann test had been found positive. The Wassermann reaction had been again positive in 1925 and he was treated with arsphenamin and mercury. For fifteen years previous to coming here he had had attacks of gastric disturbance during the spring and fall, lasting from two to three weeks. They seemed to be characteristic of chronic peptic ulcer because of dull, aching pain in the epigastrium which would occasionally radiate posteriorly, appearing two hours after eating and being relieved by alimentation and alkalis. Nausea and vomiting were occasionally associated with this distress. He would lose weight during the attacks and regain it in the interval. In 1920 the symptoms were more marked. At that time he also experienced an occasional sharp pain at the right costal margin, which radiated posteriorly to the right subscapular area and was accompanied by nausea and vomiting. This discomfort would appear irregularly after meals and was not relieved by food or alkalis. He noted residual soreness, but there was no history of jaundice or severe colic. In 1921 a Lyon biliary drainage was done and a soft diet instituted. The patient remained quite well for about a year thereafter. The symptoms then returned with greater intensity and the pain at the right costal margin was more pronounced. Exploration was performed elsewhere and a chronically inflamed appendix and the gallbladder containing stones were removed. So far as could be determined there was no definite evidence of an ulcer in the stomach or duodenum. After a short period of relief the original epigastric symptoms returned with greater frequency, but were somewhat milder. In March, 1926 hematemesis and melena occurred.

The patient was well nourished and well developed. He was obviously anemic, pus could be expressed from the tonsils, and there was moderate pyorrhea. On deep inspiration the spleen was palpable about three finger-breadths below the costal margin. The prostate was slightly enlarged and tender. The hemoglobin was 53 per cent, the erythrocytes numbered 4,400,000, and leukocytes 5,400. The clot-retraction time was prolonged. The lymphocytes numbered 25.5 per cent and neutrophils 67.5 per cent; the platelets numbered from 90,000 to 176,000. Repeated blood smears showed an absence of plasmodia. The coagulation time was five minutes and bleeding time one and one-half minutes. The Wassermann reaction was absent in the blood serum. The serum bilirubin was 1.5 mg. and there was dye retention 3. There was no undue fragility of the erythrocytes. Gastric analysis showed a total acidity of 38, free hydrochloric acid 18, and quantity 70 c.c. A roentgenoscopic examination revealed a deformity of the duodenal cap, which was apparently due to adhesions or an ulcer.

While under observation the patient had a discomfort which seemed characteristic for ulcer and which was ameliorated by the regimen followed for ulcer and by alkalis. Business matters required the patient's return home, and while there he was again given neosalvarsan and mercury. He

continued to complain of epigastric disturbances and in addition had occasional sharp pains in the left middle portion of the abdomen, radiating to the back. Because of their association with the epigastric pain they might have had some relation to the ulcer present rather than to thrombophlebitis or infarction of the spleen. In addition, there was a low-grade fever, itching, and one attack of melena. The laboratory investigations revealed secondary anemia, a reduction in the number of platelets, an increase in the coagulation and bleeding time, delay in clot retraction, and a slight increase in the retention of dye. The spleen was somewhat enlarged and there were veins on the back suggesting compensatory collateral venous circulation. The percussion area of hepatic dulness was decreased. A second roentgenoscopic examination revealed deformity of the duodenum, apparently the result of an ulcer.

Comment.—To arrive at an exact diagnosis, determine the actual source or cause of the hemorrhage, decide whether this was a single or multiple lesion, and to outline the proper therapeutic measures was obviously difficult. The anamnesis seemed convincing for duodenal ulcer, although a competent surgeon had been unable to demonstrate an ulcer at the original operation three years previously. Moreover, our first examination disclosed gastric subacidity and the cap deformity found on roentgenoscopic examination was interpreted as adhesions or ulcer. The persistence of the characteristic epigastric distress and associated phenomena after removal of the gallbladder and the appendix strengthened the diagnosis of ulcer. The evidence of disease of the liver and spleen was evidenced by splenomegalia, anemia, dye retention, decreased area of hepatic dulness on the last examination, increased coagulation time and bleeding time, delay in clot retraction, pruritus, suggesting dissociated jaundice, and enlarged veins on the back, significant of compensatory collateral circulation. The history of malaria, syphilis, and cholecystic disease further strengthened the possibility of cirrhotic changes in the liver and possibly a malarial or syphilitic spleen. The hemorrhage could result from one, several, or all the factors present. As regards the liver-spleen syndrome one could not satisfactorily differentiate between primary portal cirrhosis and associated malarial splenitis, Banti's disease, or even more remotely, syphilitic cirrhosis and splenomegaly. At operation, on August 28, 1926, cirrhosis of the liver,

of the Laennec type, was revealed. The liver was about one-half normal size and the spleen was three or four times normal size. There were greatly enlarged veins in the median line which had to be tied frequently. There appeared to be an inactive duodenal ulcer, but there were so many adhesions at the site of the old operation that there was no way of carefully examining the duodenum. A Talma-Morrison type of operation was preformed, the omentum being sutured into the wound. There was little if any free fluid in the peritoneal cavity. The prognosis as regards cure was not favorable.

Case 3.—A man, aged thirty-four, came to the Clinic complaining of hemorrhages from the stomach. For about twenty years he had had occasional spells of dyspepsia, characterized at times by heartburn and vomiting. With the exception of tonsillitis and pleurisy he had had no other disease of importance. His story was rather indefinite, but there was apparently some relief from his digestive disturbance after taking soda. In 1915 he had suffered an acute attack of gastro-intestinal disturbance which was diagnosed as ptomain poisoning. The stools were dark and small amounts of a black gastric content were vomited which the patient believed contained altered blood. Four years later he again suffered from pain in the epigastrium and vomited; there was occasional diarrhea and the stools sometimes contained blood. For about a week following this attack he experienced slight epigastric pain. Six months later he had a similar experience. He again vomited blood and noticed tarry stools. He felt slight pain in the back and on two or three occasions he lost consciousness. At that time he complained of no definite epigastric distress. In 1921, six years after the onset of symptoms, he began losing weight, and occasionally felt slight supra-umbilical pain which usually reached its maximal intensity three or four hours after meals. At rare intervals he experienced rather acute transitory colicky pain in the same area, which was temporarily relieved by food and soda. Between 1921 and 1925 there were similar periodic spells. Two months before admission, several days after one of these attacks, during the course of which he felt very weak, he vomited blood and passed some tarry stools. Since that time he has experienced almost constant, although slight, epigastric distress.

The patient was thin and slightly pale. He had lost considerable weight. The heart and lungs were apparently normal. The abdomen, with the exception of slight tenderness over the entire hypogastrium, revealed nothing abnormal. The blood pressure was normal. The hemoglobin was 78 per cent, and the erythrocytes numbered 4,400,000. A complete differential count revealed nothing of significance. Platelets numbered 168,000. The calcium time, coagulation time, and bleeding time were within normal limits. Careful investigation revealed no evidence of blood dyscrasia. Roentgenologic study showed no evidence of a deformity of the stomach and duodenum and the chest and colon were also negative. Gastric analysis revealed a total

content of 150 c.c., total acidity 70, and free hydrochloric acid 54. Because of the history of dyspepsia complicated by hemorrhage operation was advised. Exploration revealed a small hemorrhagic spot on the anterior surface of the duodenum and considerable stippling about the duodenum which was suggestive of duodenitis. Ulcer was not demonstrated. The cap of the duodenum was excised and gastroduodenostomy was performed. The appendix was found to be chronically inflamed and was removed.

Roentgenograms of the alveolar processes were made, although the patient wore upper and lower plates. A few root tips were found. These were removed aseptically and cultures were made. Three animals were injected intravenously with the emulsions and they all manifested duodenitis within twenty-four hours. There was an interesting similarity between the general characteristics of these lesions and those found in the patient at operation.

Comment.—The clinical and the bacteriologic investigations which we have conducted during the last eighteen months tend to justify the conclusion that there is a group of cases illustrated by this case in which infectious lesions are probably responsible for gastro-enteric hemorrhages.[6]

The anamnesis is usually not characteristic of ulcer, but the hemorrhage, single or repeated, and the symptoms presented, usually lead to a presumptive diagnosis of peptic ulcer. In more than half the cases roentgenoscopic examinations show no abnormalities. The gastric acidity is variable, usually not as high as in the calloused ulcer. In many cases an acute infection, such as tonsillitis, adenitis, or arthritis, has occurred just prior to the hemorrhage. Usually dense peripyloric or periduodenal adhesions, an edematous condition of the duodenum or stippling are found at operation, rarely a gross ulcer. MacCarty and Judd have described the microscopic and gross characteristics in cases of duodenitis. If the operation is performed very shortly after the occurrence of hemorrhage, acute lesions are demonstrable in the potential areas of peptic ulcer. If the operation is postponed, very little is usually found to account for the bleeding. In the majority of cases we are able to reproduce identical lesions in the experimental animal by intravenous injection of organisms obtained from cultures, usually streptococci obtained from the foci of infection. Gratifying results have been produced by removing all foci, usually dental and tonsillar, and by

instituting strict dietetic and alkaline treatment for ulcer. This has made surgical interference unnecessary.

Case 4.—A man, aged forty-five, entered the Clinic May 28, 1925 with a history of periodic dyspepsia of fifteen years' duration, which was characteristic of duodenal ulcer. At no time had there been bleeding, acute pain, the retention type of vomiting, or other evidence of complication. In the last two years, however, the exacerbations had become more frequent and the discomfort more marked.

Fig. 51.—Deformed cap. Duodenal ulcer. (May 28, 1925.)

The hemoglobin was 70 per cent, the erythrocytes numbered 4,550,000, and the leukocytes 7,400. The normal weight was 145 pounds, and at the time of his examination it was 138 pounds. The gastric acidity was normal, and the roentgenoscopic examination revealed a normal stomach but a deformity of the duodenal cap. At operation June 3 gastro-enterostomy was performed, because of a duodenal ulcer on the posterior wall about 2 cm. below the pylorus which had recently perforated and was adherent to the pancreas. The head of the pancreas was edematous over an area of 4 cm.

The patient returned in December because of weakness, dyspnea, questionable melena, and constipation. His appetite was somewhat impaired,

but he had experienced no actual pain. The symptoms had appeared gradually after two months of good health following the operation. His weight was 141 pounds. Barring anemia, tachycardia, and a small adenomatous goiter without hyperthyroidism the physical examination was satisfactory. Achlorhydria was present in all fractions, also bile and occult blood. The hemoglobin was 32 per cent, the erythrocytes numbered 3,510,000, and the leukocytes 7,600. Following a transfusion the hemoglobin was 58 per cent and erythrocytes 3,450,000. The benzidin and guaiac tests for occult blood in the stool were repeatedly positive on a meat-free regimen. Roentgeno-

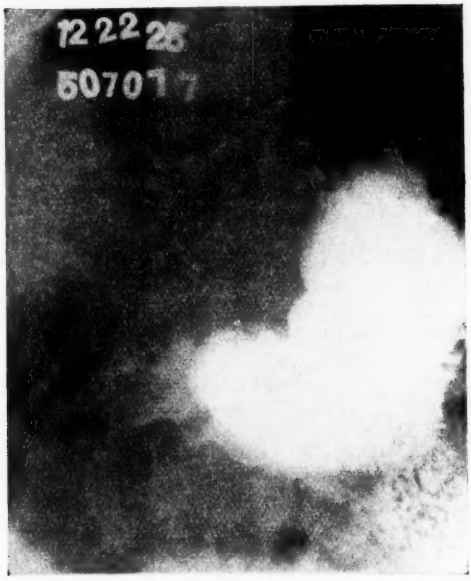

Fig. 52.—Same case as in Figure 51. Deformity of pars pylorica apparently caused by adhesions to abdominal scar. Anastomosis free. (December 22, 1925.)

scopic examination showed no abnormality about the anastomosis or in the body of the stomach. There was a deformity of the pyloric end of the stomach, apparently caused by adhesions to the abdominal wall. A roentgenogram of the colon and a proctoscopic examination revealed normal conditions. Gastric carcinoma was suspected, but following three transfusions the patient improved to the extent that his request to go home January 18 was granted.

The patient returned to the Clinic in March, 1926, because of the persistence of the original gastric symptoms in addition to epigastric disturbances and occasional vomiting of large amounts of bile-tinged fluid, mixed with

food particles. He also had subjective sensations as though the stomach emptied with difficulty when he was active in the upright position. No gross blood had been noticed. The patient was anemic, his weight was 139 pounds, and on examination of the abdomen a small mass, moving on respiration, was present at the median line just below the ensiform region. Gastric analysis revealed gross fresh blood, absence of free hydrochloric acid in all the fractions, but neither the Boas-Oppler bacillus nor retention of the motor meal. Roentgenoscopic examination revealed what was apparently a small

Fig. 53.—Same case as in Figure 51. Small ulcer on posterior wall of stomach near pylorus. Anastomosis free. (March 20, 1926.)

benign ulcer on the posterior wall of the pars pylorica (Figs. 51, 52, 53). The hemoglobin was 39 per cent, and the erythrocytes numbered 3,640,000. A clinical diagnosis of carcinomatous ulcer was made. At operation an inoperable carcinoma of the pyloric end of the stomach was found and corroborated by microscopic examination.

Comment.—This case is a digression from the main theme, because there was occult blood rather than macroscopic bleeding from the upper digestive tract. However, the circumstances of events were unusual, as gastric carcinoma is rarely closely

associated with duodenal ulcer. Moreover, the rapid development of an inoperable malignant gastric condition soon after an operation for duodenal ulcer, in a stomach apparently, from a clinical, roentgenologic, and gross anatomical standpoint, not harboring a lesion, is very unusual. Judging from past experiences it is reasonable to presume that either the duodenal ulcer has extended to the pylorus and undergone malignant transformation on the gastric side, or, what is more likely, a malig-

Fig. 54.—Niche of perforated benign ulcer on lesser curvature, pars media.

nant lesion in the pyloric portion had been present from the outset. I recently called attention to the fact that small malignant ulcers giving no symptoms or signs of their presence were accidentally found during operation for tangible benign gastric lesions (Figs. 54–57), or discovered by the pathologist in an examination of the resected portion of the stomach.

Late postoperative hemorrhage is of much diagnostic significance, especially if there has been no bleeding prior to operation. It invariably connotes the formation of a new ulcer,

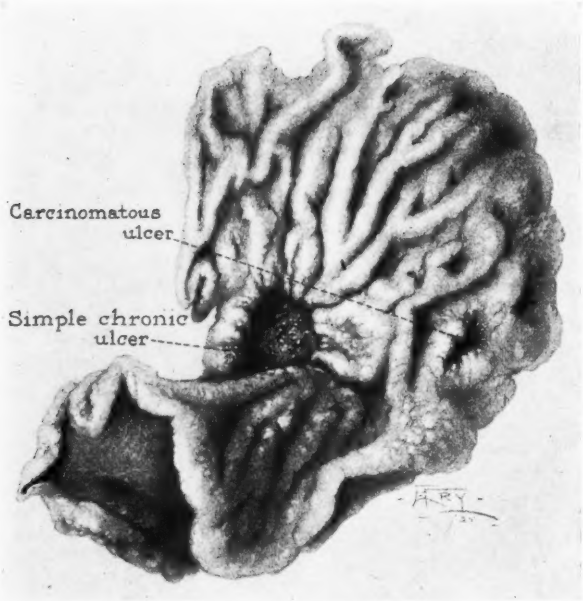

Fig. 55.—Resected specimen; benign ulcer 2 cm. in diameter and carcinomatous ulcer 1.5 cm. in diameter. (Same case as in Fig. 54.)

Fig. 56.—Two perforated ulcers on lesser curvature of stomach.

especially an anastomotic or jejunal ulcer if gastro-enterostomy had been performed. A rarer cause is a primary or secondary form of carcinoma. Associated hemophilia, purpura, hepatic cirrhosis, or splenomegaly, especially Banti's disease, may be the cause of future hemorrhage, and the prognosis must be guarded. In about 10 per cent of duodenal ulcers with a pre-

Fig. 57.—Excised specimens. Carcinomatous ulcer 2.5 by 2 by 1 cm. and a benign ulcer 1.5 by 1.5 by 1 cm.

operative history of bleeding hemorrhage may recur after gastro-enterostomy alone. In some cases this complication was remedied by removal of foci of infection. Postoperative hemorrhage in the gastric ulcer that has bled is practically obviated through excision and gastro-enterostomy or resection of the lesion.

SUMMARY

Four different types of case are presented in which anemia and bleeding from the upper digestive tract were outstanding features. In this group they were associated with cholecystic disease, with regional hepatitis and appendicitis, hepatic cirrhosis and splenomegaly, with probable associated duodenal ulcer, hemorrhagic focal duodenitis, and gastric carcinoma developing soon after gastro-enterostomy for duodenal ulcer.

Extragastric causes for hematemesis and melena, even in the ambulant patient, are as frequent as, or more frequent than, intrinsic ones. Illustrative cases are cited. Attention is called to a focal type of hemorrhagic, gastric, or duodenal lesion which promises to solve some of our problems in relation to recurrent hematemesis or melena in the absence of demonstrable gross lesions in the upper digestive tract.

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DISSOCIATED JAUNDICE

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In cases of jaundice due to obstruction of the extrahepatic biliary ducts and in that due to intrahepatic disease, that is, toxic or infectious jaundice, all the constituents of bile are dammed back to some degree and are forced to make a detour to reach temporary sites of excretion. Bile contains a pigment, bilirubin, the salts of bile acids, cholesterol, and also inorganic salts and water. The supplementary mechanisms for excretion, of which the kidney is chief, are able to dispose of the water and inorganic salts, but bile pigment and bile salts pile up in the tissues. The accumulation of pigment colors the tissues yellow. The retention of bile salts is perhaps of greater importance, since the toxic phenomena associated with obstructive jaundice, namely, pruritus and delay in the coagulation of the blood, are attributed to bile salts. In some instances icterus is associated with very little pruritus, or there may be intense pruritus with relatively little icterus. When there is appreciable retention of bile salts without icterus or without enough retention of pigment to be discernible in the skin or sclera, the condition of "dissociated jaundice" is present. The term is a little confusing, since the word "jaundice" by derivation and usage implies a yellow staining of the tissues. Nevertheless, the conception that there may be considerable variations in the relative quantities of the several bile constituents present in the tissues in hepatic disorders assumes clinical significance. Methods for measuring the quantity of bile salts in tissues and body fluids are as yet under trial, and, until further data are accumulated, it will be impossible to be sure that a quantitative relationship exists between the amount of bile salts in the blood and

the degree of pruritus. There are, however, recent methods of study which assist materially in the recognition of disorders of hepatic function, and the cases presented here illustrate the clinical value, in certain cases of pruritus, of the van den Bergh reaction of bile pigment and the Rosenthal-Rowntree method of estimating the functional activity of the liver.

Bilirubin is normally present in the circulating blood of man and gives a slight yellow color to the serum. If the van den Bergh reagent is added to a solution containing bilirubin, a purple color develops which is much deeper and more striking than the yellow tinge. The quantity of pigment present may be estimated by comparing the color obtained in a measured quantity of serum with standards representing known amounts of bilirubin. Besides being more easily read and more sensitive than the icterus index the result of the van den Bergh reaction is not affected by such pigments as carotin. Moreover, the van den Bergh reaction gives qualitative as well as quantitative information. Bile pigment is derived from broken-down hemoglobin and is elaborated outside the liver in areas in which reticulo-endothelial cells are abundant, particularly in the spleen and bone marrow. It is carried to the liver by the general circulation and is excreted in the bile. The pigment molecule reacts differently with the van den Bergh reagent before and after its passage through the parenchymal cells of the liver. Since blood serum normally contains bilirubin which has not reached the liver, it does not give a purple color with the van den Bergh reagent until alcohol has been added. Alcohol presumably separates the pigment molecule from interfering proteins by precipitating them. This idea of the action of alcohol is supported by the fact that if other protein precipitants are used, for example, a solution of ammonium sulphate, the same effect is produced. The phenomenon described is known as the indirect van den Bergh reaction. In hemolytic jaundice the production of bilirubin, in the extrahepatic sites indicated, is in excess of the ability of the liver to excrete it and the van den Bergh reaction of the blood serum is indirect. On the other hand, if the reagent is added to bile, the purple color is pro-

duced at once, suggesting that the pigment molecule in its passage through the hepatic cell had been subjected to an influence comparable to that of alcohol, presumably a freeing of interfering proteins. Now if the serum is tested in a case of obstructive jaundice, or of toxic or infectious jaundice, by the van den Bergh method, it is found to give a direct color reaction. That is, it differs from normal serum in that it is not necessary to add alcohol to bring out the color. It may be assumed, therefore, that the occurrence of a direct van den Bergh reaction in the blood serum of man is an evidence of some disharmony in the mechanism of pigment excretion, and if a direct van den Bergh reaction is found without any marked increase in the quantity of circulating pigment it might be assumed that the hepatic cell is working under some handicap. It may, indeed, be excreting pigment to the extent of preventing visible icterus, but there is, as it were, a back-wash permitting the re-entry into the blood stream of enough transformed pigment to give a direct reaction with the van den Bergh reagent. If, therefore, the bilirubin in the circulating blood is of normal quantity but gives a direct van den Bergh reaction, it will be appropriate to submit the hepatic secreting mechanism to a supplementary test of function. This may be done by the dye method introduced by Rowntree and modified by Rosenthal. If the innocuous dye, bromsulphthalein, is introduced into the peripheral circulation it will be removed by the liver and excreted in the bile. If the liver is healthy, a measured amount of the dye will disappear from the circulation within definite time limits. Delay in the rate of removal of the dye indicates lessening of the functional activity of the liver. The degree of inhibition of such activity may be conveniently recorded in arbitrary grades, 1, 2, 3, and 4.

Case 1 illustrates the possibilities of the combined methods of investigation. The blood serum of a patient with intense pruritus showed a normal quantity of bilirubin, but the van den Bergh reaction was direct and there was dye retention 3. The association of these phenomena points to the parenchymal hepatic cell as the site of the underlying disturbances. We have been

unable to show conclusively that the pruritus is due to the presence in the tissues of an increased amount of bile salts.

REPORT OF CASES

Case 1.—A farmer, aged forty-one, was under observation from September 24 to December 5, 1925. Fifteen years previously he had suffered from catarrhal jaundice. Nearly all his life the stools had been rather loose and light colored. He was certain this had been the case during the last six years, and that the urine was a little dark. As long as he could remember spells of mild diarrhea had occurred three or four times yearly. The present illness, severe generalized pruritus, began in January 1925 (nine months previous to admission). This had kept him awake at nights and he had lost weight. He had consulted several dermatologists. Whenever the stools became loose the pruritus seemed improved. In March, 1925 he had had an acute respiratory infection for two weeks, during which time the pruritus ceased.

The patient was asthenic. The skin was dry and rough and showed factitial dermatitis. There was no jaundice. The liver and spleen were not enlarged. The tonsils were infected. The systolic blood pressure was 92 and the diastolic 54. Urine showed a trace of bile salts and bile pigment. The hemoglobin was 74 per cent; the erythrocytes numbered 4,380,000, and the leukocytes 8,000. Fragility of the erythrocytes was normal. The Wassermann test was negative. The stools contained bile pigment, but were free from parasites and ova. One fractional meal showed absence of free hydrochloric acid except 4 units in the final specimen. On another occasion the total acid was 72 and free hydrochloric acid 58. The van den Bergh reaction was direct and quantitatively the serum bilirubin was 1.1 to 2.4 mg. for each 100 c.c. Test of hepatic function showed dye retention 3.

During the time the patient was under observation he was given a high carbohydrate diet. Duodenal drainage by the Lyon method was undertaken repeatedly, with a good flow of clear golden-yellow bile, but no improvement in the complaint. Other therapeutic measures employed were general diathermy and diathermy locally over the liver, applications of olive oil to the skin, alkaline baths, oxgall by mouth, hydrochloric acid, thyroid extract, and emetin. Tonsillectomy was also performed. Finally calomel, 2 grains daily in divided doses, was given. The stools became darker and the pruritus disappeared entirely for a week. The calomel was discontinued and after a few days the pruritus returned, but only to one-half the former severity. Shortly after this the patient returned home. He was sleeping and eating better and was gaining in weight and strength. We have heard from him repeatedly and his course has been variable. Under the direction of his local physician, emetin and calomel have been continued intermittently with gradual general improvement and lessening of the pruritus. Cirrhosis of the liver with dissociated jaundice was diagnosed.

Case 2.—A housewife, aged fifty-four, came under observation February 25, 1926, and was dismissed April 23, 1926. Aside from the major

complaint the past history was unimportant. In 1921 she had noted a gradual onset of generalized pruritus and it had persisted since. In February, 1923 moderate jaundice with light colored stools and dark urine developed in association with an aggravation of the pruritus. In April, 1923 an exploratory operation was performed elsewhere, with essentially negative findings. Following this the jaundice diminished slightly. In July, 1924 a second exploration was carried out for the same symptoms, and the gallbladder was drained. It contained bile and some sandy material. The fistula discharged a moderate amount of bile for three weeks and then closed. Following this the jaundice and pruritus again became worse, and in January, 1925 a third exploration was undertaken. The gallbladder appeared as a small nubbin and contained no bile. A fibrous scar along the hepatic duct seemed to be producing slight obstruction. The common duct was not identified. After the operation a transfusion was given. Following these procedures the patient improved 50 per cent. Some color appeared in the stools. The general health was good, but the pruritus persisted, and this was the presenting symptom at the time of examination at the Clinic.

The patient was in good general condition. The skin was thick, dry, and darkly pigmented. There was slight scleral icterus. The liver and spleen were not palpable. The urine showed a trace of bile. Hemoglobin was 60 per cent; erythrocytes numbered 3,780,000, and leukocytes 5,000. The Wassermann test was negative. Bile was present in the stools. The blood serum gave a direct van den Bergh reaction and quantitatively contained from 3.6 to 5.2 mg. of bilirubin for each 100 c.c. Test of hepatic function showed dye retention 4. The patient was under observation for a considerable time during which various methods of relieving pruritus were tried. These included the application of general diathermy, the administration of calomel and glycocoll, and local applications, but were without results.

March 31 the abdomen was explored. The gallbladder appeared as a small nubbin and contained bile, but no calculi. A probe was passed into the cystic duct. The common duct could not be isolated. Since sufficient scar tissue was found around the common duct to produce definite mechanical obstruction, the gallbladder was anastomosed to the duodenum. Convalescence was uneventful. On dismissal slight jaundice and some pruritus were still present. Probable primary cirrhosis with jaundice was diagnosed.

Case 3.—A Polish Jew, aged fifty-seven, a peddler by occupation, came under observation September 2, 1925. The past history contained nothing of importance. Five years and two years previously he had suffered attacks of epigastric pain of fifteen to twenty minutes' duration from which he had obtained relief by application of heat. Three years previously he first consulted a physician because of diffuse abdominal discomfort and distress across the back. Nine months before admission he began to suffer from severe generalized pruritus, which had persisted. For this he had consulted a dermatologist. Three months later painless jaundice appeared and remained continuously. The stools were white and the urine dark. The patient had lost much in strength and about 25 pounds in weight, although there had

been no further loss in the last three months. He knew the liver had been enlarged for six months.

The patient was moderately emaciated and rather deeply jaundiced. The liver was enlarged to the level of the umbilicus and was irregular, hard, and not tender. The spleen was slightly enlarged. The urine contained a trace of albumin, bile, and a few hyaline and granular casts. The hemoglobin was 70 per cent; the erythrocytes numbered 4,100,000, and the leukocytes 7,400. The differential leukocyte count was normal. The total gastric acids were 40 and the free hydrochloric acid 20. Blood urea and blood sugar were normal. Fluoroscopic examination of the stomach was negative. Determination of the serum content of bilirubin on three occasions showed 17.8, 11.3, and 12 mg. for each 100 c.c. The van den Bergh reaction was direct. Test of hepatic function by the bromsulphthalein method showed retention 4. Biliary cirrhosis with jaundice and splenomegaly was diagnosed.

Case 4.—A housewife, aged thirty-nine, was under observation repeatedly between 1919 and 1926. She had had typhoid fever at nineteen. At the time of her first admission to the Clinic in 1919 she had been married three years and there was one child, aged two. From 1905 to 1916 she suffered periodically with dyspepsia varying in onset from immediately after to one or two hours after eating, which was relieved by milk and charcoal. In 1916 she had considerable abdominal pain and acute hematemesis on one occasion. Following this the abdomen was explored and the appendix removed. This had relieved the indigestion. When first seen, in August, 1919, she was complaining of generalized pruritus of three years' duration. This had commenced during the latter half of pregnancy, and had been continuous, but with exacerbations and remissions. It was worse in the hands and feet and especially troublesome in warm weather. Slight jaundice had also been present. General weakness had been a prominent symptom since her delivery.

Examination was negative except for scratch marks and slight enlargement of the liver, the lower border extending from 1 to 2 cm. below the right costal margin. There was slight dermatographia. The urine was normal. The hemoglobin was 70 per cent. The Wassermann test was negative. In January, 1921 the patient returned, in the seventh month of her second pregnancy, complaining of rather marked jaundice of three weeks' duration with associated light colored, loose stools. The pruritus had continued. For two weeks she had noted subdermal hemorrhages, epistaxis and hematuria, with pain in the renal area. She was deeply jaundiced and the liver was slightly enlarged. The uterus was enlarged to the size of a seven months' pregnancy. The systolic blood pressure was 118 and the diastolic 80. The urine showed a large amount of albumin, bile, and a few red blood cells. Blood urea was 52 mg. for each 100 c.c. Hemoglobin was 38 per cent; the erythrocytes numbered 2,300,000 and the leukocytes 12,000. Coagulation time was twelve and one-half minutes. The Widal test was positive. Cultures of the stools and duodenal contents were negative for the bacillus of typhoid. Calcium lactate was given by mouth. Three days after admission

premature labor started, terminating in a breech delivery and moderate postpartum hemorrhage.

A transfusion was given on two occasions. Convalescence was slow, but the patient gradually improved. Probable early biliary cirrhosis was diagnosed. Toxic hepatitis associated with pregnancy and typhoidal infection of the biliary tract were also considered. In March, 1921 the patient had gained somewhat in weight, but still showed slight icterus. Hemoglobin was 69 per cent and the erythrocytes numbered 4,170,000. In July, 1921 the patient again returned on account of continuation of the pruritus. Her appetite, digestion, and bowel function were normal. Slight icterus was present and the liver was easily palpable. The spleen was not enlarged. Probable cirrhosis was again diagnosed. In August, 1922 she again returned with the same symptoms and exploration of the liver and biliary tract carried out September 11, at which time a chronically diseased gallbladder with papillomas was found and removed. The common duct was free and contained normal-appearing bile and no stones. The liver showed slight hepatitis, being slightly enlarged and soft. The pancreas was also slightly enlarged. The spleen was normal in size and appearance. There were a good many adhesions in the upper abdomen. Convalescence was uneventful. By December, 1922 there had been a steady gain in weight and strength, and the skin was clearer. Hemoglobin was 63 per cent and erythrocytes numbered 4,460,000. In June, 1923 the patient was still gaining and did not tire as easily. Hemoglobin was 76 per cent, and erythrocytes numbered 4,640,000. In November, 1925 she suffered an acute upper respiratory infection which was followed by rather deep jaundice. She returned for further observation in April, 1926 on account of the persistence of the pruritus (now of ten years' duration), which had been more severe during the previous two years. There was also considerable exhaustion, although the weight was normal. The skin was dry and somewhat darkly pigmented and showed many scratch marks. The liver was further enlarged, the lower border extending 6 cm. below the right costal margin. The spleen was enlarged and readily palpable. Systolic blood pressure was 114 and diastolic 80. Urinalysis was negative. Hemoglobin was 75 per cent; the erythrocytes numbered 4,320,000 and leukocytes 6,300. Fragility of erythrocytes was normal. Roentgenograms of the chest were negative. The van den Bergh reaction was direct and quantitatively the serum bilirubin was 1.6 mg. for each 100 c.c. Test of hepatic function showed dye retention 3. Biliary cirrhosis with dissociated jaundice was diagnosed. Because of the beneficial results of calomel on the pruritus in other patients she was given 2 grains in divided doses daily for a week, during which time the pruritus practically disappeared. Improvement continued and all pruritus ceased. Recurrence is avoided by use of 2 grains of calomel two or three days each week. The patient's general condition has also improved.

Case 5.—A Jewish housewife, aged thirty-nine, came under observation July, 1926, complaining of generalized itching and burning sensation of two years' duration. This had commenced during the latter half of the last pregnancy. It was very troublesome, especially in winter, as heavy clothes

aggravated the burning distress. It prevented sleep and was more marked around the genitalia and anus. Various physicians had been consulted. Slight scleral icterus had been noted. There had been no indigestion, colic, chills, or fever. In March, 1926 the patient had contracted a severe "cold" with fever, and during this time she was free from discomfort.

The patient appeared in good health. The skin was dry, thick, rough, and darkly pigmented. The sclerotics showed slight icterus. The edge of the liver was just palpable. The spleen was not enlarged. Urinalysis was negative. The hemoglobin was 67 per cent; the erythrocytes numbered 3,800,000, and leukocytes 6,700. The differential count was normal. The Wassermann test was negative. No parasites were found in the feces and bile was present. The van den Bergh reaction was direct and quantitatively the serum bilirubin was from 1.5 to 3.1 mg. for each 100 c.c. Test of hepatic function showed dye retention 4. Biliary cirrhosis with dissociated jaundice was diagnosed.

The patient was given 2 to 3 grains of calomel daily in divided doses for about three weeks; the pruritus ceased and the burning sensation disappeared from the extremities, but not from the trunk, especially if heavy clothes were worn. The patient was dismissed with instruction to take sufficient calomel each week to keep herself free from prutitus.

SUMMARY

A few cases of pruritus may be definitely brought into relationship with disturbed hepatic function by the methods of study outlined here.

In all of these cases pruritus was the major complaint, and had been present for months before any other symptoms appeared. The general health of the patients was good otherwise. Jaundice was marked in Case 3 and had never been present in Case 1. In Case 2 there was mild jaundice on examination, and on several previous occasions it had been prominent. In Case 4 deep icterus had been present on several occasions, once during the second pregnancy and once after an upper respiratory infection. In Case 5 slight scleral icterus was noticeable. Definite enlargement of the liver was present in two of the five cases and slight to moderate splenomegaly in the same two cases. The liver, biliary tract, and spleen were explored in two cases at the Clinic. In one case exploration had been carried out on three previous occasions. The van den Bergh reaction in all cases was direct. The serum bilirubin in three of the cases was normal in amount, although abnormal qualitatively. In

Case 2 there was slight elevation of the serum bilirubin content, and in Case 3 moderate elevation corresponding to the degree of the icterus present. In all cases the grade of dye retention was high. This is to be expected of Case 3 in which there was frank icterus, and possibly in Case 2 in which there was mild icterus. However, in the other three cases this test disclosed definite impairment of hepatic function, and in Case 1 gave the first hint that the liver was affected and was the evident cause of the pruritus. We believe that in all cases of generalized pruritus not explainable on other bases hepatic function should be investigated. Pruritus preceding painless jaundice by weeks or months is important diagnostically, indicating that the lesion producing the icterus is intrahepatic, that is to say, a disease of the polygonal hepatic cell itself. It is, therefore, not remediable by surgical means. Having discovered the site of the physiologic disharmony we are faced with the problem of influencing, by stimulation or otherwise, the functional activity of the parenchymal cell. There is little precedent to guide us in this and progress will probably be attained by a trial of various agents selected empirically. Neither local applications nor diathermy were of value in the cases under discussion. We have tried emetin empirically in some instances in this group because of the good results obtained in cases of other types of hepatic disease that could not be proved to be of amebic origin. The results have not been decisive, although we are still using the drug. In an effort to find something that would help these patients calomel was tried. Two grains were given daily in divided doses of from $\frac{1}{4}$ to $\frac{1}{2}$ grain. Contrary to custom, we have not given any saline laxative later. No diarrhea has been produced and no other symptoms of toxic effects have been noted. In Case 4 the patient after having suffered from pruritus for ten years was promptly relieved. She is taking 2 grains daily two or three times a week. It is now four months since the treatment was started and no untoward effects have been noted. In Case 5 the pruritus was relieved, but a moderate amount of burning distress persists. The patient is at least 80 per cent improved. In Case 1 the patient has continued to take emetin

and calomel and when last heard from was 75 per cent relieved. In Case 3 calomel was not tried. In Case 2 it was given for a short time without results. The mechanism of the action of calomel in these cases is unknown. There was no evidence of syphilis or dysentery, and in Case 4, in which pruritus had been present ten years, no emetin was given and complete relief followed the administration of calomel.

MYXEDEMA AND ADENOMATOUS GOITER

HENRY S. PLUMMER AND SAMUEL F. HAINES

This case is reported because it supplies a link in the chain of evidence leading to the assumption that adenomatous tissue in the thyroid gland may elaborate thyroxin independently.

The patient, a woman aged fifty, registered at the Clinic, December 21, 1923. She complained chiefly of varicose veins and ulcers of both legs of three years' duration. She had known for twenty-five years that her thyroid gland was enlarged, and for the last five weeks had taken from 5 to 7 drops of an iodin solution three times a day. For two years her weight had increased gradually; perspiration had become scanty, and speech and physical and mental activity had become gradually slower. For the three months previous to admission she had noted anorexia, and had been troubled by slight constipation, flatulence, and gaseous eructations, especially after eating greasy foods. She had been under observation in the Clinic in 1891, when an operation had been performed for varicose veins of the left leg, and again in 1917, when a subtotal abdominal hysterectomy had been performed for multiple uterine fibromyomas.

The patient's weight on admittance was 206.4 pounds (93.8 kg.). The hair and skin were dry, and there was scaling of the epidermis of the legs. The subcutaneous tissues generally were thickened and there was edema of the face. The appearance of the patient was typically that of myxedema. The right lobe of the thyroid contained a spherical adenoma 4.5 cm. in diameter; the gland otherwise was not palpable. There was a small ventral hernia in the surgical scar on the abdomen. There were varicose veins of both legs, with several ulcers on the left leg and a small one on the right leg. The systolic blood pressure was 130 and the diastolic 80. The pulse rate was 84. The urine was normal, the specific gravity was 1.033. The phenolsulphonephthalein test was 25 per cent on two occasions. The blood urea was 40 mg. for each 100 c.c. of blood. The blood Wassermann test was negative. The hemoglobin by the Dare method was 77 per cent, the erythrocytes numbered 4,570,000, and the leukocytes 6,100. A differential count of 200 leukocytes and an examination of blood smears were negative. Fractional gastric analysis showed a total acidity ranging from 30 to 48 c.c. and free hydrochloric acid equivalent to 20 or 35 c.c. N/10 sodium hydroxid. Roentgenograms of the chest showed a slight shadow in the upper mediastinum which was interpreted as substernal goiter. The basal metabolic rate was −23 and −22 per cent on two occasions. After the patient's

admission to the hospital further basal metabolic rates varied from −15 to −25 per cent, the average being −19 per cent. On January 12, 1924 5 mg. of thyroxin were given intravenously. The edema of the face began to disappear rapidly and the semblance of myxedema disappeared. Three days later the basal metabolic rate was 0, and there had been a loss of 3.08 pounds (1.4 kg.) in weight. This was probably accounted for by the loss of fluid from the tissues. Beginning January 20, 2 grains of desiccated thyroid were given daily. The basal metabolic rate fluctuated between +5 and +8 per cent until February 9, when it began to rise slowly; on that day it was +14 per cent. On March 24 it had increased to +27 per cent, and the dose of desiccated thyroid was reduced to 1 grain daily. On April 11 the basal metabolic rate was +39 per cent and the administration of thyroid was stopped. The patient had left the hospital at this time; she complained of weakness in the legs when walking. In spite of stopping the thyroid the basal metabolic rate remained elevated, and April 21 was +26 per cent. Subsequent tests of the basal metabolism showed the following rates: May 1, 1924, +33 per cent; May 12, +28 per cent; June 2, +29 per cent; July 23, +17 per cent; October 10, +13 per cent; February 19, 1925, +14 per cent, and February 23, +8 per cent. At the time of the last observation there was no feeling of weakness and there were no complaints.

The evidences of myxedema presented by this patient on admission were definite, although the picture was not that of complete myxedema. Following the elevation of the basal metabolic rate to normal the patient's own gland began to produce gradually increasing amounts of thyroxin. It is probable that adenomatous tissue in the thyroid may, under certain circumstances, elaborate and deliver thyroxin to the tissues, which probably happened in this case. That thyroxin was produced and delivered to the tissues by the patient herself is suggested by the height to which the basal metabolic rate rose, and is proved by the length of time necessary before the basal metabolic rate fell to normal after the administration of desiccated thyroid was stopped. The basal metabolic rate in this case did not reach a normal level until nine months after the thyroid was stopped. It is, of course, impossible to know definitely whether this thyroxin was produced by the thyroid gland or by the adenoma it contained. However, there is no reason to assume that a thyroid gland, once damaged to the extent of producing myxedema, should again resume its function; at least, this phenomenon has not been noted in other myxedematous patients.

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THE DIAGNOSIS AND TREATMENT OF CERTAIN GLANDULAR DEFICIENCIES

LEONARD G. ROWNTREE AND ALBERT M. SNELL

The glands of internal secretion are concerned with growth, development, nutrition, and metabolism. They may be looked on as "regulators of metabolism," but with regard to their exact function there are but few facts and many fancies.

The outstanding established data with regard to these glands may be summed up in a few words. They elaborate one or more active principles which affect physiologic activity. The hormones, or active principles, are excreted into the circulation and exert a specific action elsewhere in the organism. Disease of one of the glands may lead to increase, decrease, or disturbance of its activity, and this, in turn, may be manifested by acceleration, retardation, or perversion of the physiologic functions of the body. Disease may result from lack of a specific hormone and, in certain instances, may be cured by replacement with a hormone of the same characteristics; or an excess of hormone may cause disease which may sometimes be amenable to treatment through surgical procedures.

In spite of the voluminous literature on the subject of organotherapy, only one principle of treatment has proved entirely successful in practice, and that is the replacement of a partially or completely missing hormone by one of the same nature. Although this method has been successfully applied to at least three or four diseases, it is not effective as yet in all diseases which are due to glandular deficiency. We shall present here a series of seven cases in which the patients were suffering from glandular deficiency, and shall discuss the treatment employed and the results obtained.

REPORT OF CASES

Case 1. Thyroid deficiency (myxedema).—The first case is that of a woman, aged forty, a resident of Cuba, whom we first saw in November, 1925. She had been ill for more than five years, but had never been entirely incapacitated. At the beginning of her illness she complained only of weakness. On examination at that time she was found to be anemic; she did not respond to the usual treatment and was subsequently given desiccated thyroid by her physician, Doctor Agramonte, of yellow-fever fame. The drug caused generalized aching, tremor, and other unpleasant symptoms, and was consequently discontinued. She then began to suffer from vague neuromuscular pains, exhaustion, and occasional diarrhea. She had gained weight slowly, but her general condition had not improved. She had been examined by many physicians, and the possibility of Addison's disease and portal cirrhosis had been considered.

At the time of the patient's examination at the Clinic she was obese, and her skin was dull, dry, and pasty yellow. Her memory and attention were unimpaired, but she was exceedingly weak and listless. There were no other significant physical findings; the systolic blood pressure was 100, the diastolic 60, and the pulse and temperature were subnormal. Complete laboratory examinations revealed a low basal metabolic rate (−31 per cent on two occasions), marked anemia, and achlorhydria. The hemoglobin was 40 per cent and the erythrocytes numbered 3,600,000. We could find no evidence of hemolytic anemia by a study of the serum bilirubin, urinary pigments, or duodenal contents. The blood volume index was rather high, but no other findings suggestive of primary anemia were encountered. Neurologic findings were entirely negative.

A diagnosis of myxedema was made and treatment instituted. All of the patient's complaints responded to thyroid medication, but the anemia persisted. However, under intensive treatment she improved gradually, and was dismissed from observation after four months in Rochester. Both the blood count and the basal metabolic rate were normal.

We have heard from the patient frequently, and she has remained in good health.

Discussion of case.—It is a curious fact that this disease, which is often recognizable at a glance and which responds to treatment in such a dramatic fashion, should escape detection for so long. The elusive quality of myxedema has long been remarked by physicians of experience. Our principal reason for presenting this case is to discuss the treatment, the results, and the differential diagnosis, especially with reference to the anemia so commonly observed in such cases. Nephritis, which is most often mistaken for myxedema, may be excluded. Primary anemia presents much greater difficulty in the diagnosis. In

this case it was not possible to rule it out entirely, but in view of the absence of hemolytic features, of cord changes, and the characteristic picture of blood regeneration, it seemed unlikely. The extreme resistance of the anemia to treatment may have been due to the long-continued low maintenance diet on which the patient had subsisted for five years.

Two other conditions which may be confused with myxedema and frequently tax our diagnostic resources are moderately low basal metabolic rates and achlorhydria in patients with lowered vitality, dry skin, and pasty complexion. Plummer believes that these cases cannot be properly considered as true examples of myxedema, although some of them respond fairly well to thyroid medication. They probably represent an inherent nutritional disorder in which the normal stimulus to thyroxin production is diminished or lacking. Pituitary adenomas are frequently associated with lowered metabolism and dry, lifeless skin. We have seen a few such cases in which the general appearance was strongly suggestive of myxedema, but the concomitant symptoms of intracranial disease served to establish the diagnosis.

Little need be said regarding the treatment of myxedema. The use of a potent thyroid preparation or of thyroxin affords the best example of successful substitution treatment. According to Boothby and Plummer, the plan of treatment consists first in raising the amount of available thyroxin in the tissues to the normal concentration by one or two large doses, and second, in maintaining this level by the daily administration of an appropriate dose. An initial dose of from 5 to 10 mg. of thyroxin intravenously, or of from 2 to 4 gm. of desiccated thyroid by mouth, will usually bring the metabolic rate to normal within from three to ten days. They find that 1 to 2 grains of desiccated thyroid is the proper maintenance dose, although it may be difficult to determine this point, and prolonged observation may be necessary. It is well to warn patients of the discomforts which follow the administration of thyroid, since they are borne with much less complaint when they are anticipated. It is significant that these symptoms caused the patient in this case

to discontinue the drug in 1921, thus prolonging her illness for five years.

Case 2. Chronic parathyroid deficiency.—A woman, aged fifty-four, was first seen at the Clinic in July, 1921. She had had a large goiter for twenty years and arthritis for five years.

On examination a large adenomatous goiter, with definite signs of hyperthyroidism, was found. The pulse was 140; the systolic blood pressure was 170 and the diastolic 95. There was definite chronic infectious arthritis involving particularly the upper extremities. Thyroidectomy was advised, but the patient decided to return home without further treatment. She returned to the Clinic three years later, complaining of marked general weakness and extensive deformity of the joints. Thyroidectomy had been performed elsewhere shortly after she visited the Clinic, and three days after the operation she had had cramps in hands and feet, which drew her fingers together and rotated her hands inward, flexing them on the wrist. After about fifteen minutes the cramps disappeared spontaneously. She had several attacks of this type over a period of about three weeks following the operation; thereafter they were less frequent. She could not remember what changes were noted in the lower extremities or whether she had generalized convulsions. Each attack was preceded by prodromal symptoms of extreme warmth, tingling sensations in the hands and feet, and twitching of the muscles of the face. Since the operation the patient had been on a general diet with a good deal of milk and vegetables, but she did not remember taking calcium preparations. As she recovered from the thyrotoxic state and the immediate effects of the operation she noticed rather marked weakness and nervousness. The arthritis also seemed to become worse, and for a period of nearly three years she had been almost totally incapacitated. Tonsillectomy, performed a year after thyroidectomy, had been of no benefit.

Emaciation, weakness, and muscular atrophy were striking. The arthritis had undoubtedly progressed, but there was no serious deformity except that of the hands. There was diffuse opacity of the lenses of the eyes. The pulse rate was 88; the systolic blood pressure was 174 and the diastolic 102. There was mild secondary anemia. The hemoglobin was 69 per cent (Dare) and the erythrocytes numbered 3,880,000. The basal metabolic rate was +3 per cent. Other laboratory tests were negative. Roentgenograms of the hands and right knee showed definite destructive arthritis. An orthopedic consultant believed that the arthritis was hardly sufficient to account for the disability, and advised that the patient go to a hospital for further observation and treatment. While at the hospital a positive Chvostek's sign was demonstrated, but Trousseau's sign was absent. The blood calcium was found to be 4.8 mg. for each 100 c.c. A diagnosis of parathyroid tetany was made and treatment instituted at once.

Calcium lactate was given in large doses and the patient improved remarkably, although her blood calcium did not rise above 6.7 mg. At the time of her dismissal she was able to get about without assistance. Chvostek's sign persisted, but there were no other evidences of tetany. She continued

in fair health at her home, but returned at our request in April, 1925, for trial treatment with Collip's parathyroid extract. An attempt was made to study calcium balance, but tetany reappeared as soon as medication was interrupted. The tetany was promptly controlled by the parathyroid extract. Notes on the blood calcium levels and dosage are shown in Figure 58.

Clinical improvement was definite, although 14 gm. of calcium lactate by mouth and 5 c.c. of parathyroid extract subcutaneously were required daily to maintain her blood-calcium level. An interesting feature was the marked decrease in excitability of the peripheral nerves, as measured by electric reactions. The patient returned to her home in remarkably good condition and continued treatment under the supervision of her home physician. We saw the patient again in November; at this time she had a mature

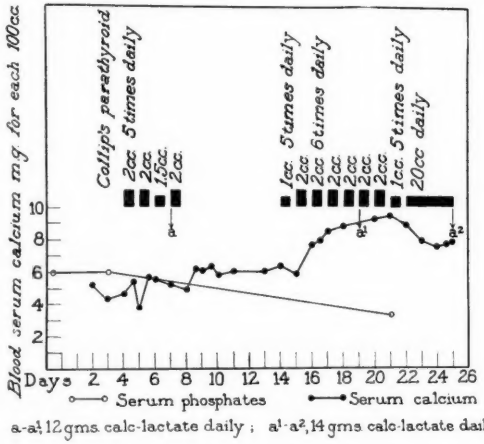

Fig. 58.—Blood calcium in a case of parathyroid tetany under treatment with parathormone (Case 2).

cataract in the right eye and an immature one in the left. She had become very despondent, due chiefly to failing vision and weakness, and objected to the frequent hypodermic injection of parathormone as well as the use of calcium lactate. Chvostek's and Trousseau's signs were present; the electric reaction showed greatly increased excitability of the peripheral nerves, and the blood calcium ranged from 5.4 to 6.5 mg. for each 100 c.c. There were no other serious symptoms, however, and December 7 a mature cataract was extracted from the right eye. During her stay in the hospital she had taken calcium lactate in doses of 15 to 20 gm. daily and seemed fairly comfortable. Her blood calcium is 8.5 mg., this level being maintained without the use of parathormone. We have advised her to take calcium lactate in the same dosage with 15 c.c. cod liver oil daily.

Since her dismissal a number of blood calcium determinations have been made. In March, 1926 9.7 mg. was reported; in May it had risen to 10.5 mg. Her physician reported definite improvement in her general condition. In August he reported that she was free from symptoms and was receiving no medicine. Her blood calcium at that time was 9.6 mg. for each 100 c.c.

Case 3. Acute parathyroid deficiency.—The second case of tetany is that of a graduate nurse, aged thirty-three, who was seen at the Clinic in November, 1925. She had had a good-sized adenomatous goiter for nearly twenty years.

The systolic blood pressure was 134, the diastolic 90, and the basal metabolic rate was −2 per cent. Laboratory studies were essentially negative. Thyroidectomy was advised and, November 10, multiple degenerating adenomas were removed under ethylene anesthetic. There was a slight postoperative febrile reaction; the patient was restless and complained of inability to use her hands properly. The following morning her attendants noted twitching of the facial muscles, and about thirty-six hours after the operation severe generalized muscular contractions, particularly of the extremities. The patient was very restless, slightly cyanotic, and breathed with difficulty. Typical carpopedal spasms were noted, the hands assuming the obstetrical position. An emergency test for blood calcium showed 7.2 mg. for each 100 c.c. Treatment was begun at once with 40 units of parathormone and calcium lactate, 4 gm., every two hours. The patient was greatly improved the following day and the dose of parathormone was reduced to 25 units. On each of the two following days 20 units daily were given. There were no further evidences of tetany; the blood calcium was 10.1 mg., and it seemed safe to discontinue the parathormone, particularly since it was producing sharp local reactions. Two days later the paresthesia which had preceded the first attack reappeared and twelve hours later tetany again developed. Treatment was resumed; 20 to 30 units a day of parathormone and calcium lactate, 12 gm. daily, maintained the blood calcium within normal limits. This treatment was continued until the patient was dismissed to continue it at home.

The subsequent course of this case was very interesting, but unfortunately is too long to be given in detail. It illustrates very well the difficulty of keeping up treatment in which hypodermic medication plays a prominent part. Many changes in dosage were necessary, and a number of attacks of mild tetany followed temporary reduction in dosage. It seemed to us that the patient was abnormally sensitive to low blood calcium, although careful study of the electric reactions did not entirely bear this out. She improved slowly, however, and in June, 1926 was able to get along comfortably without parathormone, her blood calcium varying from 8 to 9 mg. for each 100 c.c. She is now receiving full doses of calcium lactate, cod liver oil, and thyroid extract, 1 gm. daily. It is of interest that this treatment was found effective and was used successfully long before the discovery of the active principle of the parathyroid glands.

Discussion of Cases 2 and 3.—These two cases are good illustrations of the general course of true tetania parathyreopriva. The cause is, of course, removal of, or accidental injury to, the parathyroid bodies. Occasionally, we see cases of so-called idiopathic tetany with lowered blood calcium and similar physical findings, but with no history of the thyroid having been removed. Such cases are of unknown origin and difficult to classify. From them must be excluded gastric tetany, spasmophilia, and related disorders. Postoperative tetany forms a distinct group, which is characterized by alkalosis, low blood chlorids, and high blood urea, and demands a special type of treatment consisting of the administration of large amounts of sodium chlorid solution. Tetany is a relatively infrequent complication after thyroidectomy, and it is rarely that the more severe and lasting forms are observed. The symptoms and signs are well known and need scarcely be repeated here. The cramps are sometimes mistaken for rheumatism, and the paresthesia which is such an important part of the complaint has often been dismissed as of no importance. The classical Chvostek's and Trousseau's signs are somewhat inconstant, but the heightened electric excitability of the nerves and the lowered blood calcium serve to establish the diagnosis in a doubtful case.

Much experimental work has been done on the relation of the serum phosphates to tetany; in the chronic case the phosphates may be elevated considerably. This finding was noted in Case 2; that is, a marked decrease to a normal level occurred while the patient was under treatment. In Case 3, in which the patient suffered from acute tetany, no aberrations of phosphate metabolism were observed.

Extensive studies on animals have shown the beneficial effects of certain measures in experimental tetany. Among them may be mentioned bleeding, the oral administration of strontium bromid, lactose and galactose, milk diets, and the intravenous administration of Ringer's solution. Usually the animals recover spontaneously if they can be kept alive about fifty days, and, as has been stated, a somewhat similar phenomenon has been observed in man.

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Prior to Collip's discovery of the active principle of the parathyroids the postoperative course of patients with tetany was a very stormy one, and their subsequent existence was made miserable by frequent recurrences of paresthesia, cramps, and convulsions. The continued use of calcium lactate was of great benefit, and in many instances a tendency to spontaneous recovery was noted. The older forms of treatment, however, have been supplanted by parathormone, which controls the symptoms and raises the blood calcium. Doses of from 10 to 30 units daily are usually required, although much larger amounts may be necessary. The extracts on the market are satisfactory, but most of them are unduly irritant locally. The coincident use of calcium lactate is of considerable value, although probably not essential, if the food contains an adequate amount of calcium. Frequent estimations of the blood calcium may be necessary at first in order to avoid the serious complication of hypercalcemia. The duration of treatment is a question to be decided in the individual case; in the two severe cases described here calcium equilibrium was apparently established after a considerable period. In other patients recovery has taken place much more rapidly.

The development of cataract in cases of parathyroid tetany is common in the experimental animal, and a number of cases have been observed in man. The cataracts appear to mature rapidly, and are a serious complication. It is not known whether or not the use of parathormone will prevent their development, but it seems reasonable to assume that the maintenance of normal blood calcium would be desirable in any case. Other trophic changes occur secondary to tetany, for example, the rapid progression of arthritis in Case 2.

Case 4. Pituitary deficiency (idiopathic diabetes insipidus).—A farmer's wife, aged fifty-three, came to the Clinic in November, 1925. She had been nervous and emotional for some years, but considered herself to be in good health until 1921, when she suddenly developed uncontrollable thirst, and drank about 12 liters of water a day. She passed a comparable amount of urine. She suffered severely from a dry and swollen tongue, as well as from excessive thirst. These severe symptoms abated somewhat and, in fact, gave her little trouble until she had an attack of influenza in 1923. Fol-

lowing this she had suffered from vague abdominal pains. Polydipsia and polyuria recurred, although in a milder form than before. Her nervousness had, however, increased, and she became exhausted on slight exertion.

The patient appeared to be in fairly good general condition. The skin and mucous membranes were dry, and there was slight generalized abdominal tenderness. The systolic blood pressure was 112, and the diastolic 70. The daily intake of water was about 5 to 6 liters, and the urine output was only slightly less. The specific gravity of the urine was 1.001 to 1.005. The blood sugar was 0.10 per cent, and the blood urea 10 mg. for each 100 c.c. A test meal showed total achlorhydria; a sella ray was negative, and the basal metabolic rate was −17 per cent. A diagnosis of diabetes insipidus was made and treatment begun with 0.5 c.c. of pituitary extract (surgical*) administered subcutaneously. On this small dosage the urine output was reduced to 1700 c.c. and the excessive thirst greatly relieved. After a dose of 1 c.c. the patient had the first unbroken night's sleep in four years, her skin became moist, and there was a marked increase in saliva.

* The pituitary extract used in the treatment of these cases is surgical, which has about twice the strength of the obstetrical.

Because of the low metabolic rate and anacidity, a careful neurologic examination was made and spinal drainage performed. No evidence of a cerebral lesion could be found, however, and the patient was dismissed with a diagnosis of primary diabetes insipidus.

Pituitary extract had been administered to the patient at her home in sufficient quantities to control symptoms. In June, 1926 she wrote that her health was greatly improved and that she was contemplating a long motor trip.

Case 5. Pituitary deficiency (secondary diabetes insipidus).—This patient, a native of Alaska, was aged forty-six when she first visited the Clinic in October, 1924. She remained in Rochester for more than a year, and we had an opportunity to observe her carefully. Her illness began in 1921 with severe headaches, epistaxis, polydipsia, and polyuria. At the same time she gained weight rapidly. Her daily fluid intake had been more than 12 liters, and frequent voiding had interfered seriously with sleep.

Physical examination was essentially negative save for marked obesity and thick, dry skin. Renal functional tests and blood sugar were normal. The basal metabolic rate was −11 per cent, and the blood Wassermann reaction was positive. A diagnosis of diabetes insipidus, probably secondary to syphilitic meningitis, was made and treatment instituted. The output of urine fell from 8 liters to 900 c.c. on 1 c.c. of pituitary extract twice daily, with relief of symptoms, especially those of polydipsia and polyuria.

During the patient's long period of observation in the Clinic she was given practically every known pituitary preparation, and every conceivable method of administration was employed. No effect whatever was obtained by intranasal administration, and only two of the many brands of pituitary extract used were really effective. Vigorous antisyphilitic treatment was also carried out, but without effect so far as urinary symptoms were concerned. An attack of arthritis necessitated attention to oral foci; following

tonsillectomy the patient was violently ill, and it was difficult to control the excessive thirst and the dryness of the mouth. She returned to her home and was to continue treatment there.

The patient has written us that she is quite comfortable. She still takes 1 c.c. of pituitary extract twice daily; without it she finds it necessary to drink 10 liters of water daily. The question of obtaining active pituitary extract in Alaska has been a serious one in her case, and it has been found desirable to make large shipments to her during the summer months so that the drug will not be frozen.

Discussion of Cases 4 and 5.—There are two types of diabetes insipidus: idiopathic or functional, and secondary or organic. The first appears suddenly following fright, nervous strain, exposure, and alcoholic excesses. The second may be associated with a variety of cerebral lesions, chiefly pituitary tumors, gummas, and syphilitic meningitis; trauma is occasionally a factor. The symptoms are well illustrated by the two cases we have presented. Laboratory studies save for the well-known urinary findings are essentially negative in the first type; in the second type low basal metabolic rates are the rule. This point is emphasized in Table 1. Achlorhydria is also common in this group; changes in the contour of the sella, as demonstrated by the roentgen ray, visual-field changes, and ophthalmoscopic findings, may indicate an underlying pituitary tumor. Case 4 is the only instance in which the first type of the disease has been associated with a low metabolic rate and achlorhydria. Because of this, the patient was kept under prolonged observation. She may subsequently, of course, present evidence of some intracranial lesion.

It might be expected that vigorous specific treatment of patients with syphilis would relieve the symptoms of diabetes insipidus, but in Case 5 our best efforts along this line were unavailing. The prospect of securing relief by surgical measures for patients with pituitary tumors is somewhat better. Curiously enough, spinal puncture occasionally cures in an idiopathic case. There is some question as to whether the disease always arises from pituitary lesions. Basilar meningitis may be the etiologic factor, and in animals the disease has been experimentally produced by injury to the brain in the inter-

TABLE 1

BASAL METABOLIC RATE IN THIRTY-ONE CASES OF DIABETES INSIPIDUS

Case.	Basal metabolic rate.	Etiology and pathology.
1	− 1	Idiopathic
2	− 1	Idiopathic
3	+ 6	Idiopathic
4	+16	Idiopathic
5	+ 3	Idiopathic
6	+11	Idiopathic
7	+22	Idiopathic
8	− 8	Idiopathic
9	− 7	Idiopathic
10	− 6	Idiopathic
11	− 2	Idiopathic
12	+17	Secondary to neoplasm (acromegaly with adenoma of the thyroid)
13	−12	Neoplasm
14	−18	Neoplasm
15	+ 3	Neoplasm (?)
16	−15	Neoplasm
17	−10	Syphilis
18	−26	Syphilis
19	−10	Syphilis
20	−17	Syphilis
21	−24	Syphilis
22	+ 9	Encephalitis
23	−20	Trauma (depressed comminuted fracture)
24	+ 8	Encephalitis
25	+ 9	Encephalitis
26	−24	Pituitary adenoma (?) with hypopituitarism
27	0	Idiopathic
28	− 2	Idiopathic
29	−17	Idiopathic (?)
30	− 3	Idiopathic
31	− 7	Idiopathic

peduncular space and in the para-infundibular region of the hypothalamus.

Since treatment directed to the underlying cause is rarely successful, the principal therapeutic measure at our command is the use of pituitary extract. It is not certain that this is pure

substitution treatment, but its effectiveness is at least unquestionable. It is unfortunate that the hypodermic method of administration seems essential in most cases. In a number of our cases it has been possible to make extensive trials of oral, rectal, and intranasal administration, and to use fresh gland substance. Intranasal administration is occasionally quite successful, and should always be given a trial; however, in many cases it has been disappointing (Fig. 59).

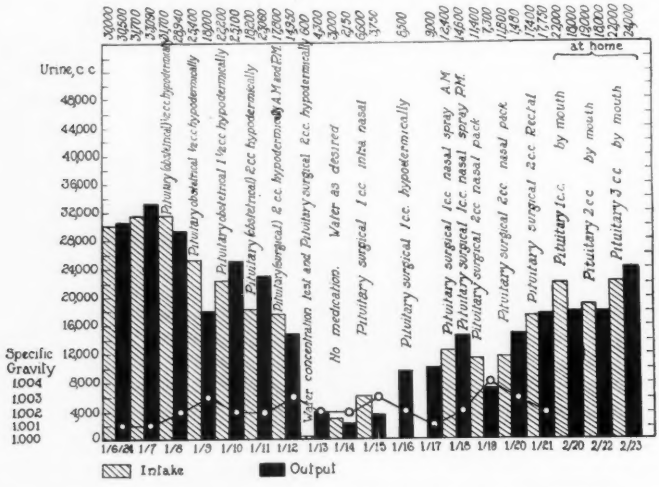

Fig. 59.—The effects of hypodermic injection and oral administration of pituitary extract in a severe case of diabetes insipidus.

The usual daily dose required to control symptoms is from 0.5 to 2 c.c. of pituitary extract subcutaneously. This dose may be divided and the time of administration varied to suit the patient's needs. Since sleep is a crucial necessity, its administration in the evening is preferable. Patients should be advised to curtail their intake of salt and water as much as they can without discomfort. The variation in response of different individuals to the various commercial preparations of pituitary extract is remarkable; this is important since a number of prep-

arations are available and should be tried in resistant cases. The remarkably active principle of the posterior lobe as prepared by Abel and his associates has given very satisfactory results in the few cases in which it has been tried.

The persistence with which treatment is carried out is, of course, a matter which the patient must decide for himself. The disease is not fatal, per se, and certainly the long-continued use of pituitary extract accomplishes nothing in a curative way. Spontaneous recovery may occur, and, as in Case 4, there may be slight remissions. It is probably wise in the doubtful cases to examine at frequent intervals, in order to detect early signs of intracranial disease. Tuberculosis and other intercurrent diseases may prove fatal.

Case 6. Suprarenal deficiency (Addison's disease).—The patient, a farmer's wife, aged twenty-five, came to the Clinic in November, 1925. She had been in good health prior to 1923, then she began to lose weight and strength gradually. In 1924 pus had been found in the urine, but this cleared up promptly under treatment. In March, 1925 she suffered from vague epigastric distress after meals. Four months later she noticed that her skin was becoming darker. The pigmentation increased rapidly for about three months; at that time she was ill with fever and general malaise. Pus was again found in the urine, but disappeared after a few days. She thought that her skin had become somewhat lighter since this illness, but her general condition was much worse and she was losing weight and strength progressively. She also had marked digestive disturbances, with nausea and vomiting.

On examination, the patient was found to be extremely prostrated and weak. The skin was bronzed, and this was accentuated at points of contact with clothing and also in exposed areas. The lips and gums were mottled bluish black. Many small dark spots of intense pigmentation were visible, especially about the face and hands. Laboratory studies were essentially negative except for slight secondary anemia, low blood sugar (0.07 to 0.09 per cent), and achlorhydria. The systolic blood pressure was 86, the diastolic 58. No evidence of tuberculosis could be obtained. A diagnosis of Addison's disease was made and the patient placed on the Muirhead treatment. Epinephrin was given subcutaneously and by rectum, with dried adrenal cortex by mouth. The patient's condition was critical from the beginning, and it was only by the most persistent effort that we were able to ameliorate symptoms. Nausea and vomiting were severe and intractable; restlessness was extreme, and she had no desire for food. Compound solution of iodin and intravenous injections of glucose have been valuable aids. After forty days in the hospital, she was considerably improved subjectively, although there was little or no change in the blood pressure or pigmentation. We used ephedrin, a drug recently introduced from China for raising blood pressure.

It is given in 0.5-grain doses by mouth several times a day. In this case, despite its effect on blood pressure, it did not prove helpful. We have given it a trial in fourteen cases of Addison's disease, but have found it of little or no value in this connection.

After the patient's dismissal she persisted in the treatment and wrote us an encouraging letter saying that she felt more comfortable in every way. After two or three weeks of favorable progress she suddenly collapsed, and died within forty-eight hours.

Case 7. Addison's disease.—The patient was a farmer, aged fifty-two, who lived near Rochester. That this case was more fortunate in its outcome may have been due, in part, to the patient's unfailing coöperation in carrying out treatment. He had been a patient at the Clinic in the past for a number of minor complaints, but in general had had no serious illness prior to December, 1922. At that time his strength began to fail and his skin, which had always been deeply tanned, grew considerably darker. Shortly afterward he had a severe attack of influenza which left him much weaker and with a severe backache. He came to the Clinic in April, 1923 very weak and deeply pigmented, especially over the exposed areas of the body. The oral mucous membranes were definitely discolored, and in the right posterior cervical region a chain of enlarged lymph nodes was palpable. A few crackling râles were heard at the apexes of both lungs. The systolic blood pressure was 110, the diastolic 80. Laboratory findings were negative save for roentgenologic evidence of pulmonary tuberculosis.

A diagnosis of Addison's disease with pulmonary and glandular tuberculosis was made and the Muirhead treatment begun. Symptomatic improvement was noted at once, and after about two weeks the patient insisted on returning to his farm work. He succeeded in doing light work for about a year and then returned for treatment of cervical adenitis. The glands proved to be tuberculous on biopsy, and were treated by excision and radium. The patient is now able to do all the work on a seventy-acre farm with comfort. He is very deeply pigmented and tires rather more easily than he did before his illness. His systolic blood pressure is 100, his diastolic 75. Until recently he has taken epinephrin by rectum and adrenal cortex by mouth; he has finally discontinued treatment and says he feels very well.

Discussion of Cases 6 and 7.—The most constant factor in the etiology of Addison's disease is, of course, tuberculosis. Simple atrophy, gummas and tumors of the suprarenal gland are but rarely encountered. In spite of the common finding at necropsy of caseous degeneration of the gland, there was evidence of tuberculosis elsewhere in the body in less than a third of the cases in our series. The incidence of previous illnesses is shown in Table 2; influenza is apparently a common exciting

TABLE 2

INCIDENCE OF PREVIOUS ILLNESS IN SIXTY-EIGHT CASES OF ADDISON'S DISEASE

Diseases.	Cases.	Series 1.	Series 2.	Series 3.
Influenza	41	12	15	14
Pneumonia	16	3	9	4
Tuberculosis (direct or indirect evidence)	15	4	4	7
Syphilis	4	1	2	1
Malaria	7	3	1	3
Typhoid fever	8	3	0	5
Trauma	3	2	0	1
Pregnancy	2	1	1	0
Nature of onset:				
Insidious	49	18	17	14
Sudden	17	4	8	5

Series 1 and 2 reported in January, 1925.
Series 3 represents cases since then.

factor, and many patients date the onset of their severe symptoms to this disease.

The symptoms of Addison's disease are well known and need not be discussed. Table 3, p. 528, contains the complaints noted in our series. Lumbar or abdominal pain and loss of weight, while not usually described in connection with the disease, are frequently present. The principal physical findings on which the diagnosis hinges are hypotension and pigmentation. In reviewing a series of cases in which Addison's disease was suspected, but subsequently disproved, this point was well brought out. In cases without definite and characteristic pigmentation the diagnosis often remains uncertain. In our experience depth and extent of the bronzing of the skin is in some respects a rough measure of the duration of the disease. In acute or fulminating cases pigmentation may be scanty and atypical or absent. Hypotension, while usually a striking feature, was absent in two cases. Laboratory data in general give but little aid in the diagnosis, and the recognition of the disease depends almost entirely on the history and physical examination.

TABLE 3

COURSE AND END RESULTS IN SIXTY-EIGHT CASES OF ADDISON'S DISEASE

	Total.	Series 1.	Series 2.	Series 3.
Progressive course prior to admission	51	18	20	13
Stationary course prior to admission	4	1	1	2
Deaths	47	16	17	14
Patients known to be living	8	0	3	5
	Incidence of symptoms.			
Symptoms:	Total.	Series 1.	Series 2.	Series 3.
Asthenia	68	26	21	21
Pigmentation	68	26	21	21
Loss of weight	58	23	19	16
Constipation	33	13	12	8
Vomiting	34	14	10	10
Nausea	29	12	7	10
Anorexia	26	13	2	11
Pain (abdominal or lumbar)	29	13	14	2
Diarrhea	9	2	4	3
Belching	12	5	2	5
Bloating	13	3	6	4
Cough	15	7	6	2
Dyspnea on exertion	26	5	15	6
Syncope or collapse	7	1	3	3

Series 1 and 2 reported in January, 1925.
Series 3 represents cases since then.

The Muirhead treatment marks a distinct advance in the management of an almost universally fatal disease. Many investigators believe that the disorder arises from lack of the secretion of the suprarenal cortex and certain experimental observations seem to bear this out. The active principle of this part of the gland has never been isolated, however, and organotherapy depends almost entirely on the substitution of the secretion of the medullary portion. Epinephrin is given frequently, twice a day or oftener, by rectum and hypodermic injection to the point of tolerance, with full doses of suprarenal cortex by mouth. The latter drug occasionally causes abdominal cramps and vomiting, and is not well borne by some of our patients. While there is some question as to the nature of its activity when given by mouth, it appears to exert a beneficial

influence in many cases. Many attempts have been made to obtain an extract of the cortex for use hypodermically, but without success. At least there is no evidence that extracts of this type are more potent than the dried preparation given by mouth.

The two symptoms of this disease which furnish the greatest barrier to therapeutic success are vomiting and collapse. The latter may be prevented largely by the avoidance of fatigue, overstrain, exposure, emotional disturbances, and strenuous examinations. Since this collapse frequently terminates fatally, the necessity for careful protection of these patients cannot be overemphasized. They should be kept warm and quiet and their strength conserved in every possible way. The active treatment of syncope is usually unsuccessful. Cardiac and circulatory stimulants, whisky, external heat, and the intravenous injection of glucose, while often of little avail, should be tried.

The control of digestive disturbances is also difficult. A proper dietary regimen consisting of small frequent feedings of concentrated nourishment, fruit juices, and caffein-containing beverages is helpful. The maintenance of adequate fluid intake is likewise of great importance. The vomiting is often attended with extreme restlessness and sedatives may be valuable. The attacks bear a striking resemblance to crises in cases of exophthalmic goiter. At the suggestion of Kendall, who called our attention to this point, compound solution of iodin was tried in one case, with gratifying results.

While the symptomatic effects of the Muirhead treatment are striking, its apparent influence in certain cases in arresting the progress of the disease is even more encouraging. Of five patients who were seen at the Clinic in 1922 and 1923, and their cases reported in 1924 (Rowntree), three are living after nearly four years. One patient, who evidenced nitritoid attacks, went into collapse and died following treatment for syphilis; the other died from intercurrent streptococcus infection of the throat which terminated fatally within two days. This patient had been seen at the Clinic in 1925, and at that time he was in ex-

cellent health, although unable to get along without treatment. Through the coöperation of his attending physician necropsy was performed and the suprarenal bodies removed for study. They were the seat of extensive caseating tuberculosis, and it was only after a prolonged search that any normal suprarenal tissue could be demonstrated. We believe that this patient probably owed the last years of his life to the Muirhead treatment, since he had failed rapidly and collapsed on each attempt to discontinue it.

In spite of most painstaking efforts, we have had many failures in the treatment of Addison's disease. This is perhaps to be expected, in view of the advanced state of the disease in many of our patients. There is also considerable variation in the individual's tolerance to epinephrin, and in many instances it is impossible to administer the drug in adequate amounts. There is no reason to believe that the treatment affects the underlying pathologic process, and at best can only counteract a functional insufficiency of the suprarenal glands. We believe that it is worthy of a continued trial, in view of the absence of more specific remedies.

CONCLUSIONS

The endocrine diseases discussed here, together with diabetes mellitus and ovarian deficiencies, represent the metabolic disorders in which we have a rational basis for organotherapy. No doubt this group will be greatly augmented, but not by the widespread empiric use of so-called glandular extracts. Polyglandular therapy is unscientific and will retard rather than accelerate acquisition of knowledge in this field. Gland transplantation, which is attracting so much attention at present, is without value in our experience. The necessity for carefully controlled clinical studies, and for a high grade of scientific skepticism in the interpretation of results, is perhaps greater in the field of endocrinology than in any other branch of medicine.

BRONCHIECTASIS IN CHILDHOOD[1]

WILLIS S. LEMON

Bronchiectasis, whether affecting children or adults, is, except in very rare instances, secondary to infections in the bronchi, lungs, or pleura. These infections may cause sufficient damage to produce the disease whether they act directly on one structure or on all combined. The latter is the more frequent. Such bacterial traumatisms not unusually eventuate in some degree of ectasis of the bronchi even though they may not be recognizable during life. This conception is not in accord with the usual teaching that bronchiectasis is a very rare disease. It implies a minimal structural damage that may even be symptomless rather than characterized by persistent cough productive of large quantities of foul-smelling sputum. It also implies an involvement of any portion of the lung and of any part of the bronchial tree, in contradistinction to the conception that it involves only the lower lobes.

Certain congenital types have been recognized and described under the titles "congenital cystic formation of the lungs" and "atelectatic bronchiectasis." These forms are of unknown etiology and are found in the fetus or in stillborn children. An acute variety described under the name "bronchiolectasis," because the anatomic site is in the bronchioli, is found in marasmic, chronically diseased children. No instances have come to our attention and they will not receive further notice in this paper; nor will I include those cases of bronchiectasis that result from aspiration of foreign bodies.

From the year 1920 until the close of 1925 approximately 15,500 children under fourteen years of age have been examined

[1] Read before the North-Pacific Pediatric Society, Victoria, B. C., June 22, 1926. Material from the Section on Pediatrics, Mayo Clinic.

in the Mayo Clinic. From among these a diagnosis of bronchiectasis has been made sixty-three times. Fifty-nine of these cases have been studied and the findings constitute the basis of this report. Death occurred in three others while under observation, and one other is included because of certain peculiarities that were thought important for illustration.

ETIOLOGY

The exact etiology of an essentially chronic disease, such as bronchiectasis, is often uncertain. It is, I think, always secondary to some infectious traumatism suffered months or years before clinical symptoms were manifest. The damage is done to the sustaining coats of the bronchi as well as to its mucosa. It may be produced as a by-product of the fibrosis. Such a conception is not out of harmony with the intrinsic or the extrinsic theories of causation or of their several subdivisions.

In the present group of patients the intrinsic damage due to inflammatory insult represents the etiologic factor. In no case was the bronchiectasis found due to extrinsic effect, such as the stenosis by pressure from malignant growth, aneurysm, gumma, or the various lymphomatous diseases.

Of the fifty-nine children under fourteen years of age, twenty-seven were males and thirty-two females. The youngest were seventeen and nineteen months old, respectively, and the oldest two were fourteen years. The duration of productive cough was taken as the criterion of disease and was found to vary from nine months in a child of eighteen months to thirteen years in a child of fourteen years. The average duration of illness was four years and four months, or a little more than 50 per cent. of the average age.

Early childhood is beset by so many serious diseases that may profundly damage the respiratory tract and they often follow each other with such surprising rapidity that more than one may seem to be responsible for the crippling effect on the bronchi. Often the responsibility was divided among several possible causes and could not be differentiated. Whooping-cough seems the most frequent precursor of bronchiectasis and

represented the causative factor, alone or in combination, in twenty-seven of the sixty-three cases.

Measles was the forerunner in eight, influenza in fifteen, frequent colds and bronchitis in nine, and pneumonia, either lobar pneumonia or bronchopneumonia, in eleven. Disease of the nose, throat, or accessory sinuses was held responsible in sixteen cases. Their rôle in etiology will be discussed later. The onset was so insidious or had occurred so long ago that the cause was unknown in five cases, in one of which the patient was a delicate child who had contracted one disease after another with great regularity and finally had had pneumonia, with empyema as its sequel. The cause of bronchiectasis in such cases is shrouded in mystery and may be the result of repeated infections, none of which are specifically responsible. In one the onset dated from severe croup and in another from convulsions. In one case the possibility of aspiration of infected material during coma was an interesting implication.

One patient developed bronchiectasis after having successfully defended himself against an acute pulmonary abscess following tonsillectomy under general anesthesia. In two cases pneumonia had developed as a sequel of tonsillectomy and bronchiectasis had developed later. In another empyema had developed; the intrapleural abscess drained spontaneously by means of a bronchial fistula. In two more bronchiectasis had resulted from pressure and consequent pulmonary fibrosis due to undrained empyema. Two patients date their illness from an attack of diphtheria, and the presence of bronchiectasis was revealed in one case at necropsy. One patient died from acute pneumonia superimposed on chronic interstitial pneumonia with bronchiectasis and was examined after death, and one other died from a gangrenous abscess associated with pneumonia and empyema.

Whatever the theories of causation, whether bronchial, pulmonary, or bronchopulmonary, it is apparent that bronchiectasis is the end result of infection deeply placed in the bronchial wall, associated with secretion and resultant increased intrabronchial pressure from cough. It can be produced by stenosis

of the bronchus if infection coexists or by gradually applied extrinsic pressure.

Relationship of disease in upper respiratory passages to bronchiectasis.—Attention has been called repeatedly, and especially in recent years, to the apparent causal relationship between the infections in the upper respiratory tract and bronchiectasis. Which infection is primary and which resultant on it has not been clearly established. We have been able to satisfy ourselves, by making use of bronchoscopic examination, in adults, that bronchiectasis subsequent to sinusitis is not quite the same in its secretory characteristics as bronchiectasis from intrinsic and primary disease of the bronchi. The bronchial secretion is less in amount, more mucoid and tenacious, and attaches itself in isolated masses on the bronchial wall. As remarked later, the predominating mucoid character of the secretion is dependent on the preservation of the mucous glands in the mucosa. The difference then in the two types is perhaps an expression of the degree of damage and of chronicity rather than of a difference in causative factors. A more complete study of the bacteriology of the disease may reveal a specificity that will supply a better explanation.

In the series of cases under discussion disease of the upper air passages occurred with surprising frequency. The relationship to bronchiectasis, however, was not at all uniform. Of forty-six cases in which the records could be depended on, thirty-two included a history of disease affecting the ear, nose, or throat that had succeeded the development of bronchiectasis, while in fourteen similar disease had preceded the damage of the bronchi.

Of the fifty-nine cases, tonsillectomy had been performed in thirty-four. Adenoidectomy had been done in twenty-seven of these, in seven tonsillectomy only, and in one adenoidectomy only had been performed. Mastoidectomy had been performed in two cases, nasal polyps removed in one, and a paranasal sinus had been drained in one other.

Among the cases in which no operative work had been done on the upper respiratory passages, advanced disease, usually associated with cervical adenopathy, was found in ten. In one

of this number partial tonsillectomy had been performed two years before the patient came to the Clinic. From among all the patients, twenty were found to have disease of the ears or nose requiring operation or treatment. These infections were variable in extent and severity. Sinusitis varied from mild inflammation to the multiple suppurative type and required varying sorts of treatment, from simple irrigation to the creation of antrum windows. Roentgenograms were taken seventeen times and were found negative only twice in the twenty cases in which nasal or aural disease was discovered by clinical examination.

It must be remembered that hyperplasia of lymphoid structures is characteristic of infancy and childhood, and that disease of these structures is so common as to constitute a very real menace to health. Had we been able to establish controls it is probable that the incidence of disease in these structures would have been found very high. Bronchiectasis may or may not develop in consequence, and alternately sinusitis, and so forth, may or may not develop subsequent to the establishment of bronchiectatic disease. That they frequently are related is dependent on the establishment of a vicious circle. Patients with bronchiectasis suffer from frequent colds, bronchitis, and pneumonia. These infections initiate or are associated with upper respiratory disease; and sinusitis, otitis, and so forth, may result. Entering the circle at another point, infections of the accessory sinuses initiate or are associated with pharyngitis, bronchitis, and the like, and may constitute the intrinsic damage to the bronchial wall that, in combination with other agents, brings about bronchiectasis. Further repeated infections, to which such individuals are prone, produce predominant disease in one or other of the anatomic areas, so that it is better to consider the diseases as fundamentally infectious and related, but not necessarily in ordered sequence.

SYMPTOMS

Those symptoms and signs associated with bronchiectasis which delineate the effect on fundamental functions of the body will be described under a separate heading. There are, how-

ever, certain symptoms that are produced as a result of the infection in the lungs, the most important of which is cough.

Cough is a very variable symptom, although it was described by every patient. It was noted that it was spasmodic, irritating, and usually nonproductive when the lesion was in the neighborhood of the hilus, and small and circumscribed. In the milder cases it started as a nonproductive cough, but became productive as the disease advanced. Even then cough was not always continuous throughout the twenty-four hours of a day, but occurred paroxysmally or spasmodically with altered position, with the patient reclining, assuming the upright position after sleep, stooping, exercising, laughing, or crying. The position producing the most productive cough was found to depend on the site of the disease and the side involved. In very young children sputum was raised only when the patient was placed in the inverted position; cough often seemed nonproductive, although, in reality, it was not so. The sputum was swallowed and could be obtained only when the excessive paroxysm brought on vomiting, a not unusual sequence.

In older children it was looser, rattling in character, and present throughout the whole year, but always made worse when a new and acute infection was superimposed. This usually occurred during the winter months or at a time when respiratory infections were prevalent. Wheezing or asthmatic breathing occurred with dyspnea in those cases complicated by marked emphysema.

Cough produces sputum of various types. It is mucoid, mucopurulent, or hemorrhagic, and may or may not be malodorous, depending on the changes in the lung from which it comes. Probably the odor in part depends on the character of the bacterial invader, but there is no evidence to prove that it does. It may depend on the systematic and adequate drainage of the bronchi and its saccular dilatations. We have noticed its disappearance after systematic training of the child to use gravity as an aid in thoroughly clearing the lung.

When the sputum has a foul odor the breath is offensive, especially after coughing. Dyspnea, cyanosis, a sense of tight-

ness in the chest, and smothering sensations are occasionally observed. Fever, malaise, asthenia, and anorexia are present in advanced cases or when moderately advanced cases suffer the added burden of acute disease.

COMPLICATIONS

The career of the patient with bronchiectasis is a checkered one. He lives for a season an uneventful life, maintaining a degree of health that has assumed the character of normal for him. It is broken by the onset of infections of many types because he is peculiarly vulnerable to infection. He is never totally free from infection and he is an easy prey to epidemic infection which produces an illness usually disproportionate in severity to its importance. Thus almost without exception these children were subject to repeated colds that were so protracted and so frequent as to be all but continuous during the winter months.

In point of frequency bronchitis rates second only to the common cold. It is more dangerous and persists for a longer time. Not all bronchitis produces bronchiectasis; the numerical ratio between the two diseases forbids acceptance of such a view.

Such acute infection superimposed on a constant one may spread laterally from the bronchus to affect the parenchyma, and pneumonia of greater or less extent results. Pneumonia is a frequent complication. In ten of this series pneumonia had occurred, and often it was repeated each winter or more than once during a single winter season.

Any disease affecting the lungs, whether acute or chronic, may also affect the pleura. Conditions are very suitable for the development of pleuritis. When once established it may take on any of the forms commonly described. There are examples of these various types of pleurisy in the present series, and they constitute the fourth complication in order of frequency of occurrence.

All the complications of empyema, such as residual pockets, open draining sinuses, and bronchial fistulas have been observed.

Abscess of the lung was the least frequent complication. Its behavior was much the same as that of empyema. It acted

in one case as the cause of bronchiectasis, but in two others it was the sequel of the chronic suppuration already existent in the lungs.

No cases of acute sepsis, brain abscess, or amyloid disease were observed, nor was there evidence of pericarditis or of endocarditis. Two cases of tuberculosis were discovered by roentgen ray, but they gave no evidence of clinically active disease and could be considered neither as the causal factor nor as a complication of bronchiectasis. The von Pirquet test was positive only twice and negative thirty-seven times. So far as these children are concerned there is no evidence to warrant connecting the two diseases causally.

Evidence of renal disturbance was not infrequent. Albumin was present in the urine twenty-four times, pus cells eighteen times, and red blood cells once. The renal change is apparently not unlike that found in any suppurative disease that is subject to recrudescence and is not to be thought a specific complication of bronchiectasis.

PATHOLOGY

In bronchiectasis the damage is essentially to the bronchi always produced by inflammation in their walls and always resulting in ectasis. Stenosis is an important factor in the production of ectasis when combined with infection. The lung itself or the pleura may or may not be involved, and the degree of involvement may be a very slight departure from normal and confined to small localized areas, or may be so wide-spread and advanced that normal architecture is completely destroyed. The bronchi, too, in cases of lesser degree may be affected but very little and throughout only a small part of their length, or they may be so badly damaged that they remain only as tortuous, stiff-walled channels serving as indifferent conduits for the flow of air to the alveoli. A general scheme, however, has been noticed and is divisible for the sake of description into four types: cylindric, fusiform, saccular, and moniliform. The last is a rare type and the second only a modification of the first.

Following the lesser bronchi throughout the lung one may find them terminating in normal, fibrotic, or emphysematous pulmonary tissue, while along their course may be seen aneurysmal dilatations of small diameter, or even one or many gross enlargements producing cavities varying in size from that of a grape to that of a small orange. Dilatation of small tubes may be so extensive as to transform the lung, giving it a honeycomb appearance.

In a study of bronchiectasis in adult patients, especially in those of advanced years, apical ectasis was observed which had been produced by the combined effect of tuberculosis and the healing processes that resulted in dense fibrosis. Long-continued cough, slowly advancing stenosis, and possibly extrinsic traction brought about the changes in the bronchial wall that resulted in dilatation. Such changes were not observed in any of the cases in this series nor can one expect them. Tuberculosis, it is true, was found to coëxist with bronchiectasis, but was pathologically unrelated and not an etiologic factor. It could not well be because, up to the age of fourteen, such fibroid phthisis is rare.

All of these lesions were basal in location. Some were confined to small localized areas near the hilus and affected one side only, but the great majority were associated with various pathologic changes affecting the lower lobes of the lung and extending peripherally and involving the pleura, which at times was densely thickened.

When the ectatic bronchus is opened a variable appearance is observed. In early cases the mucosa is inflamed, swollen and often edematous, and mucoid material in increased quantity is adherent. If the disease is more advanced the mucosa becomes paler and the secretion loses its mucoid character and becomes mucopurulent or essentially purulent, depending on whether or not the mucous glands have been destroyed. In areas of varying size the mucosa may be denuded and replaced by granulation tissue which bleeds easily. Again, it may be raised into networks of trabeculæ, or folded on itself to such an extent that it assumes a shaggy, villous appearance. Calcareous plates have

been seen in our adult cases, but not in childhood. The sacculations are usually smooth walled and gray, and contain malodorous green or greenish-yellow pus.

The microscope presents a diversified appearance from simple inflammation associated with infiltration by polymorphonuclear leukocytes or round cells in the mucosa to a complete loss of all normal appearing cells. Normal epithelium may be replaced by one of many layers and folded into masses projecting into the lumen of the bronchial tube.

Blood vessels are engorged and tortuous, frequently aneurysmal, while the wall of the bronchus is dense, organized, thickened, and stiffened by layer after layer of fibrous tissue separating and, by pressure, atrophying the muscular and elastic tissue that had given strength and movement to the bronchus. Round-celled infiltration insinuates itself throughout the wall of the bronchus extending from mucosa to adventitia. Like the muscular and the elastic coats, the cartilage may be atrophic and distorted.

The fibrous changes attended by such destruction not only to the mucosa, but equally to the muscular and elastic layers proceed toward the parenchyma. It is rare to find a lung in which the walls of the alveoli in close relation to the bronchi are not also affected. Here fibrous thickening shows itself in the alveolar walls and proceeds to the interlobular septa often joining, by that course, with fibrosis in the pleura, which in turn passes inward along the septa to the parenchyma. Except in cases of interstitial pneumonia the alveolar epithelium is unaffected. In the latter disease, however, the alveoli are obliterated by organizing connective tissue. Interstitial pneumonia may or may not be associated with dilatation of the bronchi. When lobar pneumonia or bronchopneumonia, gangrene, or abscess are complications, the pathologic changes are characteristic of those diseases. Lung abscess, however, may be confusing because it may be the intial lesion or the sequel of bronchiectasis. When the former, it has ceased to exist because of drainage and collapse of its walls, but by extension of infection from the original site or aspiration of its contents, bronchiectasis may be

produced. When a sequel to bronchiectasis, its identity may be difficult to determine. The shaggy uneven appearance and the presence of vessels coursing throughout its lumen and the occasional finding of thrombosis within them usually serve to identify the loss of substance or abscess. The wall of a bronchiectatic cavity is more often smooth and glistening, and has certain areas of denuded epithelium and others with intact mucosa whose cells may retain their cilia. The muscular and elastic tissue coats may be identified as well as remnants of cartilage, and the blood vessels maintain their anatomic relationship to the bronchial wall.

CLINICAL MANIFESTATIONS

Examination of lungs.—Pure bronchiectasis rarely exists. Physical signs are the product of the multiplicity of lesions that are associated either as causal factors or as sequelæ. A relatively small number, however, belong to this classification and the signs are those of disease in the bronchi alone. They are variable, sometimes entirely wanting, sometimes localized in a small area, sometimes unilateral, but usually bilateral. They are found over the lower lobes within the back or in the axillary regions. Auscultation alone is of value in eliciting these signs which are represented by nonconsonating râles of medium or coarse bubbling character. Nor are they always present. They may be absent entirely when the bronchi contain secretion; then the breath sounds are distant and percussion may reveal a dulness of the lung note. After the bronchial contents have been dislodged by inversion or coughing, dulness and distant breathing are replaced by resonance and normal or slightly bronchovesicular breathing; nonconsonating bubbling râles can be heard.

When the lung is to a greater or lesser extent involved in the disease and has been impaired by fibrous change, constant râles of nonconsonating bubbling type may be heard, the percussion note is dulled, and vocal resonance more intense. Vocal fremitus is of practically no value in childhood because the anatomic disproportion of the lungs makes them poor resonators of sounds produced in the larynx.

In those cases in which multiple cavitations exist and especially when they are superficial and sufficiently large, characteristic cavity signs can be found. These consist of hyperresonance, increased vocal resonance in the form of bronchophony or whispered pectoriloquy, cavernous or amphoric breathing and consonating râles, especially heard following cough.

When pneumonia is present as a complication the signs are characteristic of that disease, dulness over the pneumonic areas and bronchial breathing being the most diagnostic of the familiar findings. It is possible that they may not appear, however, when the consolidation is centrally placed and unconnected with an open bronchus. The severe illness, rapid breathing, high fever, and leukocytosis are significant features and diagnostic. Pneumonia is so common a complication that the significance of such findings is all the more apparent.

The extent of pleural disease varies greatly and may not be suspected on physical examination or may be so obvious that the intrapulmonary disease seems insignificant or impossible of recognition. There are no differences in physical findings in the mild cases from those characteristic of uncomplicated pleurisy, either acute or chronic. When the disease is advanced, however, the child's mobile chest lends itself to the most extensive deformities. The respiratory excursion is lessened, the intercostal spaces decreased in width, and the movement of the hemithorax is sometimes paradoxical in character. Curvature of the spine appears and the convexity of the curve is directed toward the healthy side. The mediastinum, the heart, and trachea are displaced laterally toward the affected side. If children deform readily, compensation takes place readily. This is apparent in the unaffected portion of the diseased lung and in the unaffected lung when the disease is unilateral. Emphysema is discovered by the increase in size of the lung, the hyperresonant character of the percussion note, and by the inability to define accurately the borders of the heart or liver. The breath sounds are bronchovesicular and in some instances sibilant or wheezing sounds can be heard.

The physical findings are as diverse as the pathologic changes producing them.

Sputum.—There is a preconceived notion that a diagnosis of bronchiectasis requires that large quantities of malodorous, mucopurulent, or purulent sputum shall be produced by cough. That such a conception is erroneous is amply proved by experience with large numbers of cases of bronchiectasis, both in adults and in children. In the latter group the exact amount of sputum is often difficult even to estimate. Before the age of five or six the child swallows sputum and does not expectorate it. Often the amount can only be approximated and is masked under the indefinite terms of: considerable, profuse, large amounts, small amounts, and so forth. Only occasionally can concrete terms be applied. In our series, with cases under observation, the amount varied from 30 to 500 c.c. in twenty-four hours. In several instances the child had to be held in an inverted position and the sputum collected before any accurate knowledge could be obtained either of the amount or character of the sputum.

No other disease of the lungs and bronchi produces hemorrhage more frequently than does bronchiectasis, and in no other are there greater variables as to amount or time of production. One reason for the frequent mistaken diagnosis of tuberculosis rests on the fact that bronchiectasis, like tuberculosis, may have hemorrhage for its initial symptom, and the hemorrhage may occur months or even a year before other signs develop. This has been true in my experience with cases in adults and was true in Case 54 of the present series. In this instance there were five hemorrhages of unknown cause before the constant productive cough and the malodorous mucopurulent sputum in amounts of from 125 to 250 c.c. helped to identify the disease. In childhood, however, hemorrhage seems relatively less frequent than in adult life. In the present series it was recorded only eight times (14 per cent). In cases accurately observed for a longer time the percentage undoubtedly would be much higher.

A foul odor to the breath is frequently observed in very young children and succeeds a coughing spell. It may occur also with older children who are better able to expectorate their

sputum. Among these were eight whose sputum was described as definitely malodorous. When present it has a character that is not soon forgotten, a nauseating foulness that pervades and remains in a room. When the mucosa is not destroyed, but retains its mucous glands, the sputum is mucoid or mucopurulent. When these glands have been destroyed by severe or long-standing disease, it becomes pure pus. In the former it has the thick tenacious character of mucopurulent sputum that keeps the product of each expectoration separate. In the latter it has become homogeneous, thin, and greenish yellow, and mixes intimately, so that the separate amounts from each expectoration can no longer be identified. Such discharge is usually the most profuse of all varieties and is almost always the most offensively malodorous.

Fingers and toes.—In cases of long standing, deformity of fingers and toes is almost a universal finding. The changes may vary from simple clubbing of the distal phalanges to actual bony overgrowth that has been described under the name of hypertrophic pulmonary osteo-arthropathy. In my experience with pulmonary suppuration in childhood the latter condition has not been observed, but various types of clubbing have been seen with great frequency. It appears in the more chronic forms, but may occur in patients whose illness has lasted for only a few weeks or months.

In well-marked cases the skin of the fingers becomes smooth and shiny like that seen in patients suffering from arthritis deformans. The terminal phalanx is enlarged in both diameters and the area overlying the matrix of the nail is elevated and usually slightly pinker in color than elsewhere. The proximal border can be elevated and made palpable by pressing downward over the distal end of the nail. These alterations in shape of the terminal phalanx cause the finger to take on such a change in contour that, when the finger is viewed laterally, the impression is obtained that the second phalanx is concave and smaller than normal. When viewed from above the terminal phalanx is broadened and the nail is seen to occupy a lessened area so that there is a wide lateral margin uncovered by nail. This is true

in those cases in which the nail is narrow and highly convex transversely. The nail, however, may be more spatulate, flattened transversely, and cover almost the whole upper surface of the broad phalanx. The deformity affects both fingers and toes, but the former in greater degree than the latter. The first three digits are more noticeably affected than the outer two. There are many variations from the classical nail with a high convexity both longitudinally and transversely. It may be markedly convex longitudinally and bend like a talon over the end of the finger, and yet be broadly spatulate and flattened transversely; or conversely, it may be narrow and highly convex transversely, but not remarkably convex longitudinally.

The color varies from normal through various degrees of cyanosis, and on a very few occasions has had a blackened appearance. In one instance the color was probably produced by a variety of Aspergillus isolated by the dermatologists. In other instances no cause for the dark color could be found, and it may have been due to atrophic changes. Dystrophy of the nails is seen rather frequently and is represented by thickening, roughness, pitting, and fragility. In Cases 26 and 34 the nails were highly convex, narrowed transversely, blackened, thickened and roughened, representative of the advanced type of change that occurs in bronchiectasis.

The theories explaining the production of clubbing of the fingers have been no more convincing than those explaining the origin of the disease itself. To obtain evidence of a positive or negative character the nail-fold capillaries have been studied and the circulation through them observed. No positive statements can be given as yet, but Roth, working in Brown's laboratory, has supplied me with the following brief preliminary report:

"Nail-fold capillaries have been examined in twenty-one cases of club-fingers. The ages ranged from five to sixty-two years. These cases were divided into age-groups and the following data obtained:

"In the younger group the capillary flow was fairly uniform and moderately fast, as seen in the normal young person. After the age of forty all the cases showed slowing of the capillary

stream and other minor abnormalities such as are seen in normal persons of the same age. There is an impression that the capillaries are a little broader both in the younger and older groups, particularly so on the arterial side in the older group, than in normal persons of the same age.

"The conclusion would be that there is no explanation in the nail-fold capillaries for the overgrowth."

Roentgenologic findings.—The roentgenologic findings depend on the character of the lesion within the lung, its location with respect to other structures within the chest, and the character of overlying structures. Thus, an early lesion may not be sufficiently dense to produce a shadow. Bronchiectasis situated in the lower lobe of the left lung might be obscured by the heart, and a thickened pleura or superimposed fluid may obscure intrapulmonary disease situated beneath it. In all there were seventy-one roentgenologic examinations made and a positive diagnosis of bronchiectasis was returned twenty-nine times. In twenty-six other cases bronchial thickening or thickening suggestive of bronchiectasis was diagnosed. Apical tuberculosis in association with bronchiectasis of the lower lobe was reported twice. There was one report of calcified lymph nodes, and negative reports were returned ten times. The remainder included a heterogeneous group in which pleural thickening, pleural effusion, and fibrosis associated with retraction of the heart and mediastinum, were the striking characteristics. The roentgenologist had no knowledge of the clinical findings in any of these cases, yet in three instances of patients clinically improved, the report at the later examinations varied with the favorable progress of the disease and was finally changed to negative. One case previously reported as thickened pleura and possible bronchiectasis was later described as bronchial thickening suggestive of bronchiectasis, then as marked bronchial thickening, and finally, after a year's time, as negative. The second had been reported as a localized area of bronchiectasis in one lobe, but four months later the report was negative. In the third case the reports varied from a primary one of bronchial thickening to localized bronchiectasis, and finally to a negative

report. Marked clinical improvement was concomitant with the roentgenologic findings of improvement.

It was noted that roentgenologic evidence suggestive of bilateral disease occurred in 44 per cent, while evidence of unilateral disease occurred in 56 per cent of the examinations. This evidence is not more conclusive of the relative frequency than that obtained by clinical examination. Like the latter, it is subject to various factors that prevent certainty in the localization of such a lesion. With the perfection in the use of opaque substances, such as lipiodol, and with the increased popularity of the bronchoscopic examination, a truer estimate will be obtained of the relative frequency of the unilateral lesion. Such examinations were not commonly made in the present series comprising those cases examined between 1920 and 1925. The maximal age was fourteen years, and the average duration of the disease only four years. It is permissible to think that in later years a much higher percentage of cases of bilateral disease will be observed.

PHYSICAL FITNESS

Because these children are able to attend to the ordinary duties of childhood, the fact that they are physically below normal is lost sight of. Exceptions to this impression were fairly common in this series. They were children whose disease had started in early infancy and had rendered them physically unfit. They were frail, undernourished, asthenic, and unable to engage in the play and activities of their classmates because of fatigue and dyspnea. Others were periodically rendered equally unfit by the occurrence of acute infection which usually attacked the child with particular severity.

It seemed advisable to inquire into the effect of the disease on the class as a whole rather than to draw conclusions from exceptional cases at exceptional periods during the course of the illness. The effect of disease, it has seemed to me, can be appraised best by studying its effect on the fundamental functions of the body. For this reason twenty-five representative cases with fairly complete records were chosen and studied in respect to their departure from normal. Height, weight, pulse rate, tem-

perature, blood pressure, and blood characteristics, including the content of hemoglobin, were considered (Tabulation, p. 549). It was thought that such a survey would give rather an accurate estimate of the physical fitness of the group.

Certain generalizations may be obtained from a study of the tabulation. It is apparent that as a group the patients are, with one exception, below the maximal height for age and sex, and that only fourteen had grown to the average height, although all had reached the minimal height. Growth in height is not seriously interfered with by this type of chronic respiratory disease. Only four children weighed more than normal for their age, height, and sex. Three others weighed more than the average for age and sex alone. All others were below average, and in the whole series of fifty-nine the average loss of weight was 7.6 pounds. The loss of weight in the tabulated group varied approximately from 1 to 31 per cent, while the average loss was approximately 8 per cent for the group normal for sex, age, and height.

The pulse rate was the most variable function studied. It was subject to conditions of excitement, posture, and to the degree of temperature. There were instances of variation as great as from 80 to 140 beats a minute. The pulse was taken with the child at rest in the sitting posture and counted for the full minute; the average for the group was 100. When the whole series was studied it was found to average 103. The discrepancy is explained by observing that the youngest members were excluded from the selected group.

The average temperature was taken while the children were ambulatory, and not during acute exacerbations of the disease. In only three in the selected group was the temperature 100° or more, but the average temperature was 99.2°. This was raised to 99.4° for the whole group in which temperatures were taken under similar conditions.

The blood pressure readings were taken in only sixteen of the selected group. The highest reading was found in a girl aged ten, and was 130 systolic and 82 diastolic. The lowest reading was found in another girl aged ten and registered only

TABULATION

THE SYSTEMIC EFFECT OF BRONCHIECTASIS

Case.	Sex.	Age, years.	Weight, pounds.				Height, inches.			Pulse. rate.	Temperature, °F.	Blood pressure:		Hemoglobin, per cent.	Erythrocytes, millions.	Leukocytes.
			Estimated normal.[1]	Average.	At examination.	Loss or gain.	Estimated normal.[1]	Average.	At examination.			Systolic.	Diastolic.			
22	M.	12	85	86.0	68	−17	50 to 65	57	58							
23	M.	12	89	86.0	96	+7	50 to 65	57	59	96	99.0	100	65	79		9,700
24	F.	10	61	70.5	54	−7	47 to 60	53	51	96	98.2	90	60	78		22,700
25	F.	5	37	41.0	39	+2	38 to 47	42	41	98	102.6			75	4.39	19,700
26	F.	8	55	56.5	49	−6	43 to 55	49	56	90	98.0	112	84	76	5.43	11,000
28	F.	12	75	90.0	70	−5	50 to 65	57	55	100	99.2	110	58	70	4.34	11,500
29	F.	12	69	90.0	64	−5	50 to 65	57	53	80	98.6	114	90	70	4.98	6,700
30	F.	14	117	108.0	120	+3	55 to 71	63	64	100	98.6	120	78	72		10,400
32	F.	10	70	70.5	69	−1	47 to 60	56	54	100	99.0	130	82	75		8,300
33	M.	13	68	94.0	69	+1	52 to 67	59	53	90	99.0			72	5.00	11,800
34	M.	9	72	64.5	69	−3	45 to 58	51	55	96	99.0	130	75	80	4.73	9,800
35	F.	10	78	70.5	74	−4	47 to 60	53	56	96	98.4	110	66	72		21,800
36	M.	12	92	86.0	90	−2	50 to 65	57	60	104	97.8	120	78	68	4.02	13,400
37	M.	8	55	57.0	47	−8	42 to 56	49	48	100	98.6			75		5,500
38	F.	12	79	90.0	60	−19	50 to 65	57	56	92	98.6			73		13,500
39	M.	9	61	64.5	47	−14	45 to 58	51		144	99.2	80	50	60	4.82	19,200
40	F.	6	42	44.5	40	−2	38 to 50	44	44	110	101.0			70	4.82	18,900
41	F.	11	63	78.5	51	−12	48 to 62	55	51	108	99.5	90	64	70		6,700
42	M.	8	55	57.0	57	+2	42 to 56	49	51		99.2			72	4.54	8,500
43	M.	7	50	52.0	42	−8	41 to 53	47	47	120	99.2			70	4.03	7,500
45	F.	7	47	51.0	48	+1	40 to 53	46	48		100.0			71		15,900
52	F.	10	61	70.5	52	−9	47 to 60	53	51	114	98.8	102	50	70	4.67	12,700
53	F.	6	45	44.5	41	−4	38 to 50	44	45	80	99.5	100	80	68		22,300
56	F.	11	74	78.5	67	−7	48 to 62	55	58		99.4	120	90	75	4.35	11,000
59	F.	6	47	44.5	43	−4	38 to 50	44	46	140	101.4	102	60	72	4.57	14,500

[1] Baldwin and Wood tables used for weight, height, and age.

90 systolic and 60 diastolic. The average blood pressure was 108 systolic and 70 diastolic in a group in which the average age was just under ten years. Healthy children of that age usually have a systolic reading of about 100 and a diastolic reading of about 64. In the whole group, blood pressure readings were taken in thirty-five. The average systolic pressure was 106 and the diastolic 69.

In the selected group the hemoglobin, estimated by the Dare method, averaged 72 per cent. The erythrocytes averaged 4,630,000 and the leukocytes 13,120. In the whole group of fifty-nine cases the hemoglobin averaged 70 per cent, the number of erythrocytes 4,420,000, and of leukocytes 12,530.

We have dealt then with children whose growth has been kept to the low average for age and sex, whose weight is reduced below normal, whose pulse rate and temperature at rest averaged about normal, and whose content of hemoglobin and number of erythrocytes were normal, but whose leukocyte count was distinctly increased to the proportions of a true leukocytosis. These findings were obtained under favorable conditions while the children were ambulatory and not during recrudescence of disease due to superimposed infections. A general estimate would be worthless if data were collected during unusual periods induced by acute disease.

It would seem justifiable to conclude that bronchiectasis is a debilitating disease that profoundly affects the fundamental functions of the affected child.

SUMMARY

The foregoing description of bronchiectasis in childhood would serve to show that the disease is not especially infrequent and that it may be looked for in those who have suffered from chronic infectious processes of the bronchi, lungs, or pleura, singly or combined. Whooping-cough, influenza, measles, and pneumonia are common precursors and act as the etiologic factor in the production of ectasis. It wouldappear that they cause intrinsic damage to the deeper structures in the bronchial wall, because secretion results and cough adds to intrabronchial tension.

From a study of the relationship of disease of the accessory sinuses evidence has been produced showing that such disease may be the van or the rear attack, the cause or result of bronchiectasis.

Instances have been shown illustrating the transformation of abscess of the lung and empyema complicated by bronchial fistula into bronchiectasis. The converse has been noted from bronchiectasis; abscess and empyema succeeded by bronchial fistula have occurred as a sequel to bronchiectasis.

An attempt has been made to indicate the protean character of the disease and to relate the physical findings and symptoms with the pathologic changes responsible for them. Finally, evidence has been collected showing the damaging effect of the disease on the physical fitness of its unfortunate victims. Not only are the children who have advanced bronchiectasis unwelcome in society, but those less severely affected are stunted in growth, impaired in strength, susceptible to epidemic infection, and handicapped for happy and productive life.

LIMITATIONS IN THE USE OF LIPIODOL IN THE DIAGNOSIS OF DISEASES OF THE LUNGS

PORTER P. VINSON AND WILLIS S. LEMON

From two to five years is usually required before a new remedy becomes universally known and accepted by the medical profession, and this is approximately true of lipiodol which was first used as an aid in the diagnosis of neurologic diseases. Its use gradually extended to the diagnosis of disease in various other organs of the body, particularly of the lungs, since it is opaque and adds precision to roentgen-ray pictures.

The four most common methods of introducing lipiodol are: the supraglottic, transglottic, subglottic, and bronchoscopic. In the supraglottic and transglottic methods the oil is introduced through a curved cannula; in the subglottic method, through a hollow curved needle which is passed through the cricothyroid membrane into the trachea, and in the bronchoscopic it is introduced directly through the bronchoscope into the trachea. We inject it through a bronchoscope.

Powdered barium was first used to outline the several parts of the bronchial tree, but lipiodol was substituted because of its blandness and consequent freedom from irritation. Roentgenograms then taken showed clearly evidence of disease in areas that remained unsuspected by inspection of ordinary plates. The use of lipiodol has finally become quite as important in diseases of the lungs and bronchi as the opaque material used by the cystoscopist in the examination of the bladder and kidneys.

In the year 1925 an increasing number of bronchoscopic examinations were made at the Mayo Clinic because it was felt: (1) that greater precision in diagnosis could be obtained; (2) that surgical indications would be more clearly depicted; (3) that the appearance of the various lesions could be noted and

appropriate treatment applied, and (4) that tissue or secretion could be obtained for examination. Inasmuch as inspection is so important in examinations, it was decided that opaque material would be used only after the bronchoscope had revealed evidence of disease and the site to which the lipiodol should be directed. Throughout the series of examinations many instances were noted in which no information of value could have been obtained had this rule been broken. Four cases from the series are recorded as illustrative of the limitations in the use of lipiodol in bronchoscopic examination.

REPORT OF CASES

Case 1.—A man, aged twenty-eight, was examined May 4, 1926. He had been well until the preceding January when a severe pulmonary hemorrhage had occurred and about 2 pints of blood were lost. Three smaller hemorrhages followed, the last occurring one month before examination. He had had a slight nonproductive cough and had lost about 13 pounds in weight. An attack of scarlet fever had occurred in March. There was blood in the urine at this time.

The general and roentgen-ray examinations were essentially negative (Fig. 60). On bronchoscopic examination, a smooth easily bleeding lesion about 5 mm. in diameter was seen on the left posterior wall of the right main bronchus just below the bifurcation of the trachea. A small portion removed for microscopic examination proved to be granulation tissue.

The patient was permitted to return home and a week later he coughed up a small amount of blood. July 9 a second bronchoscopic examination revealed a small tumor at the site occupied by the lesion observed at the first examination. The tumor was completely removed (Fig. 61) and the bleeding base cauterized with 10 per cent silver nitrate solution. Again, a specimen was examined microscopically and proved to be granulation tissue. There was no evidence of infection in the bronchial tree at either examination.

Comment.—In this particular instance, had the physical and roentgen-ray examinations been depended on the lesion could not have been located. Had lipiodol been introduced into the bronchial tree without inspection, the localization would have been equally uncertain. By bronchoscopic examination and direct inspection of the inside of the trachea and bronchus, the cause of hemorrhage was easily seen to be a lesion about 5 mm. in diameter on the left posterior wall of the right main bronchus. Following the bronchoscopic examination there was no indica-

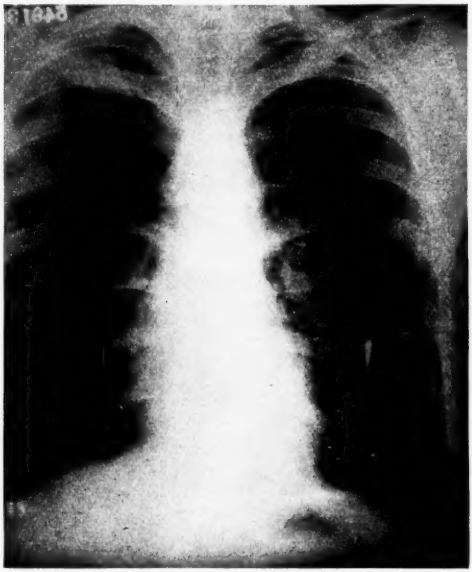

Fig. 60.—Negative roentgen-ray of chest.

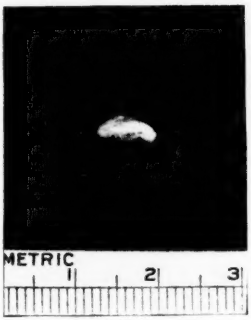

Fig. 61.—Granuloma, the source of bleeding, removed through the bronchoscope. Proved by biopsy to be nonmalignant. It had not caused obstruction.

tion for the introduction of foreign material into the bronchial tree.

Case 2.—A man, aged thirty-three, was examined December 18, 1924. He had been well until March, 1923, when he had had an acute attack of abdominal pain which was believed to be due to appendicitis. The appendix, which was removed, was not badly diseased, but there was generalized peritonitis. Cough developed two days after the operation and soon small amounts of purulent sputum, sometimes blood-stained, were expectorated. Two months later a diagnosis was made of pulmonary tuberculosis, but it was not confirmed on careful investigation at a tuberculosis sanatorium. In January acute pain appeared in the abdomen and was relieved by enemas. Two weeks later, without a preceding cold, empyema developed on the right

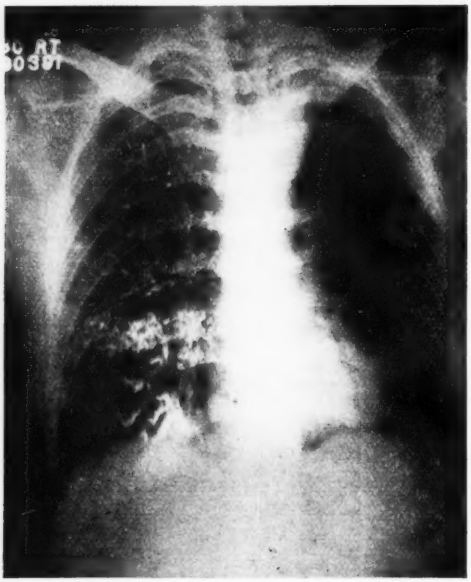

Fig. 62.—Lipiodol showing bronchiectasis of the right base.

side and a rib was resected. The wound drained for a month; then there were frequent hemorrhages from the lungs in which a teacupful to a pint of blood was lost. The hemorrhages were usually precipitated by exertion.

A superficial examination of the chest failed to reveal evidence of a gross pulmonary lesion. Roentgenograms disclosed localized bronchiectasis at the base of the upper lobe of the left lung and destruction of the anterior portion of the eighth rib on the right. Bronchoscopic examination was advised for the purpose of determining the exact source of the bleeding, but the patient declined to have it done, fearing it might precipitate another hemorrhage. However, the next day bleeding began and for four months it was profuse.

The hemoglobin was reduced from 74 to 24 per cent and the erythrocytes from 4,540,000 to 2,170,000. It was concluded that the blood was coming from the left lung and partial pneumothorax was induced. This stopped the hemorrhage for two months.

At the end of three months the patient had improved sufficiently to return home. During the trip home bleeding began and continued for four weeks. Four more severe hemorrhages occurred, but between February, 1926, when he returned to the Clinic, and May 14 there were no further hemorrhages. Examination of the chest at this time revealed a diminution in breath sounds at the bases of both lungs with bubbling râles over the same

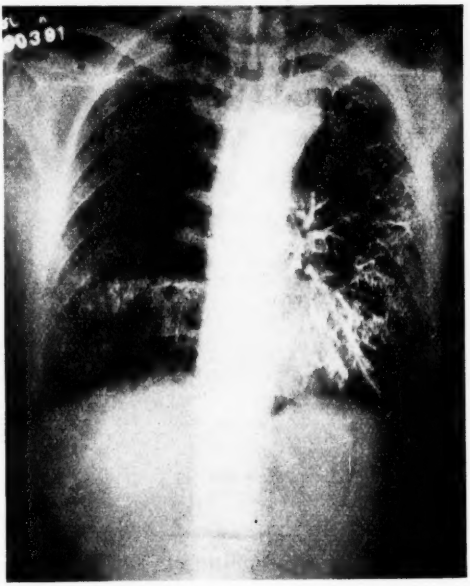

Fig. 63.—Lipiodol showing bronchiectasis of the left base.

areas. The hemoglobin was 81 per cent and the erythrocytes numbered 4,760,000. Roentgen-ray examination of the chest showed pleuritic adhesions to the left diaphragm and left costophrenic angle and bronchiectasis at the base of the right lung.

The patient returned home, but bleeding began again and a month later he came back to the Clinic. Bronchoscopic examination was then made and revealed bilateral basal bronchiectasis, but as there was no bleeding at the time the source of the hemorrhages could not be determined. The right bronchus was injected with 20 c.c. of lipiodol and a roentgenogram made immediately (Fig. 62). Three weeks later, following a hemorrhage, another

bronchoscopic examination was made and it was found that all of the blood was issuing from the bronchus of the right lower lobe. At this time 20 c.c. of lipiodol was injected into the left bronchus (Fig. 63).

Comment.—From the history and physical findings in this particular case, it was felt that there was bronchiectasis on the left side of the chest and that the diffuse hemorrhage was coming from that side, but on the patient's first visit he refused to have the bronchoscopic examination and afterward the severe hemorrhages made it inadvisable. A long period of illness followed in which the prognosis of ultimate recovery was very doubtful. The bronchi on the left side were apparently filled with blood and purulent material so that the usual sounds heard over the lung were absent. Expectoration was excessive, and dyspnea was so acute that the patient was forced to a sitting position for many weeks. During this period he had had pneumonia, and bronchiectasis developed in the right chest, presumably from aspiration. When he was finally able to leave the hospital, it was thought that the bleeding point was in the left side, because the introduction of air into that side and the production of a partial pneumothorax had apparently arrested the hemorrhage. On the patient's return, it seemed permissible to examine him through the bronchoscope and injections of lipiodol were made into the right bronchus, and later into the left. Both injections disclosed the evidence of bronchiectasis, but did not help to localize the point of hemorrhage. When the hemorrhage again occurred, three weeks after the first injection, the blood was seen issuing from the right lower lobe, which in all probability was the site of bleeding from the beginning. Had lipiodol been used at any stage of the illness, the results would have been equally unsatisfactory. It is our conviction that direct inspection of the interior of the bronchi is of paramount importance, and that the use of opaque material must be kept subsidiary to it.

Case 3.—A man, aged forty-eight, came to the Clinic April 30, 1925. For six months previous to May, 1923 he had felt tired and "ached all over." In May, 1923 it was believed that an abscess of the lung had ruptured as he coughed up a large amount of bloody, purulent material. He continued to cough and had several hemorrhages, from a mouthful to a half pint. He

also coughed up many small calcified granules. His weight decreased from 196 to 150 pounds. June 20, 1924, in a coughing spell, he brought up a piece of chewed toothpick. He continued to cough, but there was very little sputum and no more calcified granules. There were occasional periods of fever. The patient had not been able to work since the onset of his illness.

Examination of the chest showed that the right lung below the scapula posteriorly and in the right axilla was flat with poor transmission of breath sounds. There were no râles. Leukocytes numbered 18,400. Roentgenogram of the chest showed tuberculosis of the upper right lobe with dense consolidation in the lower right which was thought to be indicative of an

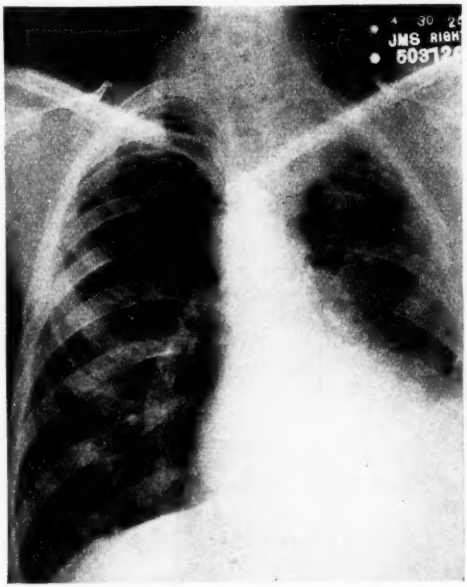

Fig. 64.—Evidence of bronchiectasis at the right base.

abscess. Bronchiectasis was noted in the right middle lobe (Fig. 64). The sputum was negative for tuberculosis bacilli. Bronchoscopic examination disclosed considerable calcareous material in the posterior division of the bronchus of the right lower lobe. Six or eight large pieces were removed (Fig. 65). The bronchial lumen was obstructed by this deposit. During the twenty-four hours following the secretions were greatly increased. Ten days later another bronchoscopic examination was made and a considerable amount of secretion was found, but no more concretions.

The patient returned July 15, 1925, markedly improved. He had worked hard since his previous visit. The sputum and cough had gradually decreased,

and he had gained 10 pounds in weight. Another bronchoscopic examination revealed considerable purulent secretion from the bronchi on the right side, particularly of the lower lobe. There was no evidence of stone formation at this examination. A letter from him three months later stated that he had coughed up another stone a month before. He was feeling well and had made a further gain of 13 pounds.

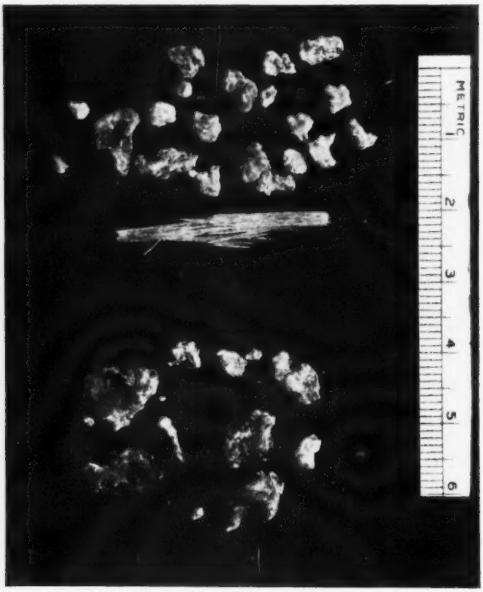

Fig. 65.—Calcareous material expelled by cough. Toothpick aspirated and later expelled during paroxysm of coughing. Large calcareous masses broken up while being removed through the bronchoscope.

Comment.—In this instance the use of lipiodol would have been valueless and, in fact, a handicap to the diagnosis. The bronchus was so filled with calcareous material as to prevent the oil from flowing into the bronchial tree, and the plates would have shown only what was already known, namely, that bronchial stenosis existed.

Case 4.—A woman, aged thirty-one, came to the Clinic January 20, 1925. In April, 1923 an impacted wisdom tooth had been extracted under local anesthesia. During the operation she felt something in her throat

and attempted to direct the operator's attention to it. She did not cough, and as the symptom did not remain after the extraction she dismissed the incident from her attention. In April, 1924, following the uneventful extraction of another tooth, she expectorated a little purulent material in the mornings, without cough. She thought the pus came from the tooth socket, but the wound had healed completely. The dentist made a roentgenogram of the sinuses with negative results. The sputum continued for four months and then stopped, but the patient complained of lassitude. In January, 1925 she developed a "cold," with pleurisy on the right side accompanied by fever. Sputum containing streaks of blood appeared once, completing a

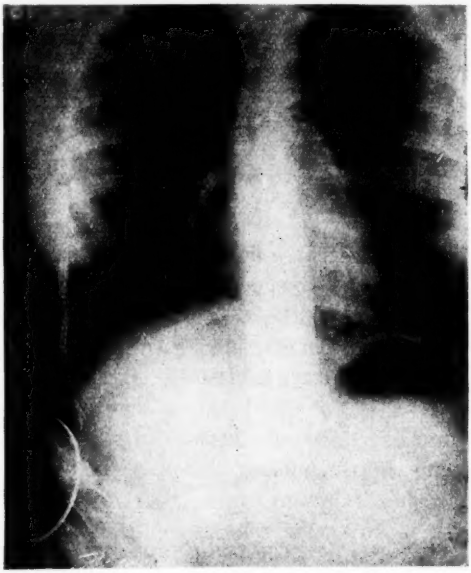

Fig. 66.—Small localized area of bronchiectasis at right base. No evidence of foreign body.

clinical picture suggestive of pulmonary tuberculosis. The patient did not improve and was sent to Colorado for ten weeks. While there the cough ceased, but fever, fatigue, and rapid pulse persisted. She returned home and was in bed until July, when she was permitted to be up for a month, but because of fever and increased density in the right lung she was sent back to bed. She spat up a small amount of blood October 11, 1925. It was finally concluded that the patient had unilateral bronchiectasis, and bronchoscopy was advised.

At one examination crackling râles could be heard over a localized area in the right axilla. Roentgenograms of the chest showed a small area of

consolidation in the right lower lobe and interlobar effusion (Fig. 66). The results of further examinations were recorded as "some improvement," "marked improvement," "infiltration in the lower lobe of the right lung, probably old pneumonia," "negative," and so forth. The sputum was negative for tuberculosis bacilli and elastic tissue. Bronchoscopic examination revealed a small granuloma on the mesial aspect of the right main bronchus, almost at the bifurcation. A tiny tip protruded. Forceps were applied and a piece of bone removed (Fig. 67). Uneventful convalescence followed.

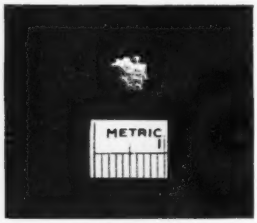

Fig. 67.—Bone removed from bronchus.

Comment.—The diagnosis in this case was particularly difficult, because of the insidious onset and the inability to discover sufficient evidence on which to base a diagnosis. There was no thought of bronchial stenosis, and for this reason lipiodol could have been used satisfactorily. It can be seen readily that lipiodol would have been of little value in view of the diagnosis of unilateral bronchiectasis. By bronchoscopic examination, and direct inspection of the mucosa, the exact site of the lesion was seen and the cause removed.

CONCLUSIONS

Aside from the history of disease and its progress inspection is the most valuable aid in diagnosis. In diseases of the bronchi direct inspection through the bronchoscope is most important, and it should be employed in all cases in which ordinary procedures fail to provide an exact diagnosis. Lipiodol is the most recent and perhaps most important aid to such inspection. We believe that no matter what method is used in the injection of lipiodol into the air passages it should not be introduced until after the bronchial tree has been thoroughly inspected through the bronchoscope.

DIFFERENTIAL DIAGNOSIS AND MEDICAL AND ORTHOPEDIC CARE OF SEVERAL DIFFERENT FORMS OF CHRONIC ARTHRITIS

PHILIP S. HENCH AND PAUL N. JEPSON

We herewith present five patients with chronic arthritis. In each the etiology, treatment, and prognosis are different, sometimes markedly so. A discussion of the medical and orthopedic treatment indicated for each patient will be given, and general comments made on the management of the various types of chronic arthritis.

Chronic arthritis and rheumatic disturbances in general are caused by the same three factors, broadly speaking, that produce most bodily disturbances: infection, irritation (trauma), or senescent or retrogressive changes in tissue. At the first approach to a case of arthritis the relation of these three etiologic factors to the individual condition must be determined. Frequently, in the individual case, the arthritis is not caused by one factor alone, but by a combination of two or all three factors. From an etiologic standpoint the recognition of the pure and mixed forms is essential not only for the institution of proper treatment, but for prognosis. Mixed forms are quite as common as pure forms such as those illustrated here.

The infectious forms illustrated are rheumatic fever and chronic infectious (nonspecific) arthritis. The irritative forms are chronic traumatic (static) arthritis from obesity, and gouty arthritis with uric acid depositions as the articular and periarticular irritant. The chronic senescent arthritic form is due to retrogressive tissue changes from the wear and tear of life.

Nomenclature.—Many different nomenclatures are available for the various forms of arthritis. Some are based on the preponderant pathologic change (proliferative, degenerative, at-

rophic, hypertrophic, and destructive); others on the anatomic structure involved (synovial, periarticular or rheumatoid, and chondro-osseous or osteo-arthritis), and others on roentgenologic differentiation (hypertrophic, destructive, periarticular). None of these directly indicates to the physician what he most wishes to know, namely, the etiology; nor can they provide entirely clear-cut distinctions, because the different clinical states do not themselves always adopt, to the exclusion of others, one form of pathologic invasion, tissue reaction, or anatomic location.

For example, the term "hypertrophic arthritis" is often used to mean exclusively a so-called purely metabolic or senescent and not infectious joint process, and yet hypertrophic bony changes are not confined to any one etiologic type of arthritis, but may occur in several etiologically different forms. In infectious arthritis (specific or nonspecific) the roentgen ray may show changes either of a pure periarticular type or of a hypertrophic or destructive type, or there may be atrophic changes in bone and cartilage. In senescent arthritis such as, for example, Heberden's nodes, the bony changes are almost always hypertrophic, though they may be destructive or only periarticular. Traumatic arthritis, acute or chronic, may be periarthritis, being in soft tissues alone, or may involve the bone, in which case hypertrophy usually occurs. In the irritative gouty form, due to the deposition of uric acid, periarticular response in the soft tissues alone may occur (in the early stages) or may proceed to hypertrophic or destructive involvement of bone.

Certain etiologic classifications are made cumbersome and lengthy by their minuteness and complete specificity. A definite simplification along etiologic lines would seem to be the one used here: infectious arthritis, traumatic (irritative) arthritis, and senescent arthritis. Such titles, by their attempt at least to indicate a direct causal association, suggest at once appropriate treatment. Obviously, in the infectious type obliteration of foci and care of metastatic infection are primarily indicated. In the irritative form the trauma, of whatever form it be, must be checked; eradication of foci is either not specifically indicated or of minor importance. In the senescent

form treatment can only be symptomatic, palliative, and to a degree prophylactic, because, representing as it does the retrogressive tissue changes of life, its causes are in the main unalterable. Arteriosclerosis and trauma seem to combine to cause this form, but even the trauma is of an indefinite unirradicable type.

REPORT OF CASES

Case 1.—This patient was a physician, aged forty-six, whose chief complaint was swelling and pain in the great toe. About twenty-five years previously he had had an attack of pain in the right ankle, with redness and swelling, which lasted about three weeks and subsided under the administration of salicylate, leaving the joints entirely free. From time to time he suffered from lumbago for brief periods. He had known that he had a cardiac murmur for years, although he did not know whether or not it came on after the first attack of rheumatic fever. He had had tonsillitis repeatedly as a child, and quinsy two or three times. Seventeen years before infectious iritis affected the left eye; two years before admission it recurred, and there have been one or two minor attacks since then. For the two months prior to admission there had been blood in the stools and duodenal ulcer was diagnosed by roentgen ray. Six weeks before admission the present attack started with marked swelling and redness of several joints. The inflammation would last a few days in one joint and then migrate to another, apparently disappearing in previously affected joints. By the time of admission it had disappeared from all areas except the great toe of the left foot. Salicylates had relieved the pain considerably. All the other systems were apparently normal and there had been no history of cardiac decompensation.

The great toe was markedly red and swollen, and there was slight stiffness and pain in the right ankle and hip. There were three abscessed teeth and considerable pyorrhea. The tonsils were fibrous and infected. The prostate was normal. The heart was definitely enlarged, and there was a loud mitral systolic murmur transmitted to the axilla. The first mitral and second pulmonic sounds were accentuated. The pulse rate varied between 80 and 100. The blood pressure was normal. The roentgenogram of the left foot was negative, as it characteristically is in rheumatic fever except for periarticular swelling. The roentgenogram of the stomach was positive for duodenal ulcer. The blood uric acid was normal.

The diagnosis was recurrent rheumatic fever with subacute exacerbation; mitral insufficiency, compensated. Treatment consisted of tonsillectomy, alveolectomy, salicylates, local heat to the affected joints, and rest in bed for cardiac prophylaxis.

Comment.—Although the patient was a physician, and although he had been warned of the presence and consequence of focal infection by the recurrence of rheumatic fever and iritis, and

the occurrence of a duodenal ulcer, he neglected the urgent need for irradication of foci. The case presents striking points in the differentiation of acute or chronic rheumatic fever and acute or chronic infectious arthritis. The characteristic points in acute rheumatic fever are the migratory type of acute articular disease (with its classical alleviation by salicylates), the marked prostration, and the very low incidence of residual articular affection, and the high incidence of residual cardiac damage with the intramural presence of Aschoff bodies. Rheumatic fever uncomplicated should leave joint function normal and should not result in chronic arthritis, although the latter does occasionally happen. It often develops that one joint in which chronic arthritis eventuates is or has been subjected to unusual trauma, which had apparently produced such physiologic changes in the joint that under the burden of acute rheumatic fever complete function is not restored. For instance, an obese patient may retain after an attack of acute rheumatic fever a chronic arthritis in the knees, because he is subjected to the marked trauma inflicted by his weight. Ordinarily, however, restoration of complete articular function after a migrating type of arthritis, which often follows acute tonsillar infection and is frequently associated with chorea and favorable response to salicylates, are differential points in favor of the diagnosis of acute rheumatic fever rather than acute infectious arthritis. The relationship between these two processes is in some ways quite close, in other ways not at all so. Reference might be made to the comparative pathology of pulmonary tuberculosis and pulmonary pneumonia. Tuberculosis leaves residual pulmonary pathologic changes, fibrosis, and so forth; pneumonia produces acute hyperemia, congestion, and so forth, and practically always entirely disappears. The former might be compared in its nature to acute infectious arthritis, the latter to acute rheumatic fever. Acute rheumatic fever, however, frequently leaves its residue in the valves and muscles of the heart, primarily as an interstitial valvulitis with vascular thrombi and perivascular inflammatory reaction, which leads to secondary destruction of valve leaflets and the formation of Aschoff bodies at

the site of focal interstitial inflammation with secondary myocardial degeneration. It would be interesting to compare the pathologic changes with the obliterating capillary lesions of infectious arthritis and to speculate on the reasons for the difference in the selective capillary lesions.

The treatment of rheumatic fever is, in brief: (1) Eradication of all foci as soon as possible; (2) intensive medication with salicylate; (3) application of oil of wintergreen and heat to the joints, and (4) the institution of a suitable regimen and prophylaxis. Regarding the latter, cardiologists are more and more emphasizing the need for the immediate institution of a regimen to include prolonged periods of rest, even in the absence of any direct evidence of cardiac damage during the acute, febrile, arthritic stage of the disease.[15] The patient should be kept quiet as long as signs of infection persist. Salicylates may be given by mouth, and if tolerated such administration is quite as efficacious as intravenous or rectal administration. With equal amounts of sodium bicarbonate and a daily fluid intake of 3,000 to 4,000 c.c. during such administration, doses of sodium salicylate up to 100 grains daily are well tolerated. In rheumatic fever, however, marked response to salicylate is classic, while in acute arthritis the relief from pain may be slight and the objective joint manifestations are practically unaffected. In rheumatic fever occasionally salicylates seem ineffective; arsenicals intravenously may then be of benefit. Special orthopedic care is not necessary. Protective cradles for affected joints are beneficial.

Case 2.—A single woman, aged sixty-four, had been working as a bookkeeper. It is of interest to note that her father died at seventy-two of some form of renal trouble, and her mother at seventy of "arteriosclerosis," both senescent diseases. Except for the direct manifestation of the present disease the patient's medical history was negative. Menopause had occurred at forty-eight. Her chief complaint was deformity of the fingers at the terminal phalangeal joints only, in both hands (Fig. 68), which she had first noticed about a year and a half before. She had observed no swelling, pain, creaking, or distress of any sort except for mild occasional tenderness on pressure. The patient requested treatment because of the cosmetic insult of the deformities, and because of worry over the possibility of general rheumatic affection.

Fig. 68.—Deformity of the terminal phalanges and Heberden's nodes in a case of chronic senescent arthritis.

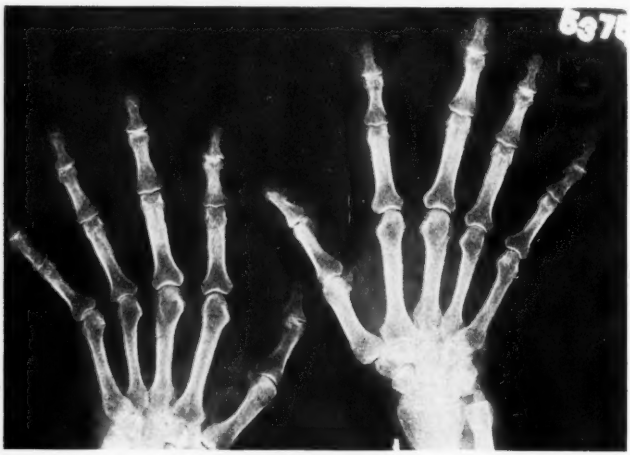

Fig. 69.—Swelling of the soft tissues of the terminal interphalangeal joints. There is slight destruction and lipping of the distal joint of the left index finger.

The systolic blood pressure was 140, the diastolic 86. The tonsils were questionably infected and plugs were present. The heart was slightly en-

larged, and there was an aortic systolic murmur with accentuation of the second aortic sound. Except for the Heberden's nodes all joints were free. The roentgenogram showed swelling of the soft tissues of the terminal interphalangeal joints (Fig. 69).

The diagnosis was chronic senescent arthritis with Heberden's nodes; aortic sclerosis. Eradication of foci was not indicated. Treatment consisted of reassurance, heat and brief massage daily, and contrast baths.

Comment.—Considerable vagueness exists concerning the exact nature of Heberden's nodes, and definitions in the textbooks vary. Heberden spoke of them as "little hard knobs," which Osler describes as "small bony outgrowths at the sides of the terminal phalangeal joints." Bradford and Lovett imply that the pathologic changes are varied, while Llewellyn and Jones do not directly state their nature. Some authors erroneously apply the term "Heberden's nodes" to rheumatic or arthritic nodes in any bodily situation. Apparently in the first stage there may be swelling of the soft tissues only, subcutaneous fibrosis localized on one or both lateral aspects of the distal interphalangeal joints, and generally initially of the fifth and index fingers, although all may become affected. The process may remain thus, and if so is generally painless except for occasional numbness or tingling of the fingers and perhaps soreness at times on pressure or bumping. The patient may not notice them for years. If the process continues to the second stage, which is associated with cartilaginous erosion and bony hypertrophy and lipping, with or without some destruction of bone, pain is generally present intermittently or almost constantly.

Concerning the patient presented, if she did not worry about the looks of her fingers, no treatment except reassurance would be given. Contrast baths, alone or supplemented by physiotherapy of a mild type, are all that seem indicated if pain is present. The contrast baths consist of immersion of the extremities in alternate containers of hot and cold water, for about one minute each, alternating back and forth for fifteen to twenty minutes in all, beginning and ending in the hot water. By the resultant alternating vascular dilatation and constriction peripheral circulation to the joint is improved.

Heberden's nodes are a form of senescent arthritis. They occur in the "physiologically old" and are more common in women than men, possibly resultant on women's handiwork. Senescent arthritis occurs in men, mostly in the lumbar spine, with the presence of incidental spondylitis of which the patients are often symptomatically ignorant. In hieroglyphic writings the determination of old age was the figure of a man bent with arthritis (Fisher). Willis found that hypertrophic arthritis of the spine was almost universal after the age of forty-five, appearing generally a decade earlier in the heavy than in the slenderly built person. Garvin has shown that in a series of 2,090 patients over the age of fifty, 67 per cent of the men and 40 per cent of the women were affected by this incidental spondylitis or senescent arthritis. A further analysis showed that 60 per cent of the women and 75 per cent of the men so affected were without any complaint of the various types of rheumatic, neuromuscular, and arthritic pains. The medicolegal aspect of senescent spondylitis is important to recognize, as pointed out by Garvin, for the proper interpretation of such a finding in a patient after industrial trauma may prevent injustice to employers. The knee joint and hips are the other general sites of senescent arthritis.

In senescent arthritis infection probably plays a minor rôle or none at all, although senescent arthritis, for example Heberden's nodes, may be often seen in elderly persons who also suffer from truly infectious arthritis. Indeed, because of the fact that persons with pure senescent arthritis are often without pain, it is usually only when such arthritis is associated with an infectious form that the physician sees patients, except incidentally, with the senescent form. The etiologic factors are probably articular vascular sclerosis and chronic trauma, accounting for the location in the spine (especially of men), the knees, and the fingers (especially of women). It is a disturbance that demands no eradication of foci, no special treatment, no fearful prognosis. Heberden's nodes are sometimes used to prognosticate longevity (Osler). They are a senescent phenomenon, and like gray hairs, moderate arteriosclerosis, mild hypertension, and

other evidences of senescence (arcus senilis, hyperprostatism), with some of which they are generally associated (as in this case aortic sclerosis), may appear sooner or later in all persons as an expression of the wear and tear of life. Reassurance that no general rheumatic disability need be anticipated is usually sufficient for the patient, although it must be noted that the process locally is likely to progress slowly with the years. The differential diagnosis is suggested in the obvious character of the nodes, the incidental nature of the arthritis of the spine or knee, the time of life, arteriosclerosis, and other signs of senescence. Mild hypertension often exists as contrasted with the hypotension and other systemic signs, to be discussed later, seen in arthritis of the truly infectious type. Chronic senescent arthritis compares to other forms of chronic arthritis as vascular diabetes or arteriosclerotic nephritis would to true diabetes or chronic glomerular nephritis of the Bright's type.

The senescent type of arthritis as recently seen in two cases is briefly as follows: The first, a woman, aged sixty-one, as a child had suffered from infantile paralysis which left the left arm partially paralyzed, although she had used it considerably for many years. She had marked Heberden's nodes with changes in the soft tissues and bone in every terminal joint of the unaffected (right) hand, while the left hand was entirely free. The systolic and diastolic blood pressure readings in the right arm were 160 and 80, in the left 120 and 70. The etiologic factors of arteriosclerosis and trauma would here seem prominent. The second patient, a woman, aged sixty-three, had complained of aching pains with Heberden's nodes for five or six years. The node on the fifth right finger had been rather red and swollen for a month, and had been lanced twice by the family physician with no relief from pain and without the appearance of pus. Here the roentgenogram showed marked bony hypertrophic changes associated with the subcutaneous hypertrophy, and thus the pain is probably accounted for.

Case 3.—The patient was a farmer, aged thirty-nine. His chief complaint was rheumatism of the left knee and foot which had been diagnosed rheumatic fever elsewhere. At the age of twenty-four he had experienced

sharp pains and swelling of the left foot for several days, after which they disappeared entirely. The following year a similar attack occurred, this

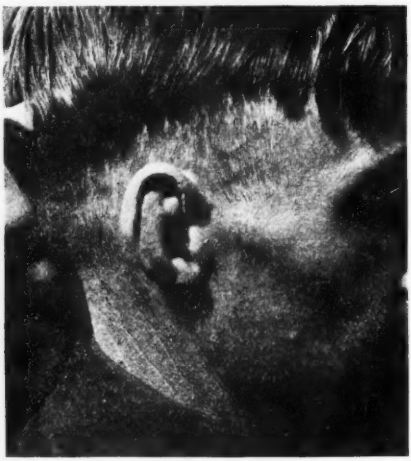

Fig. 70.—Tophi in the ear.

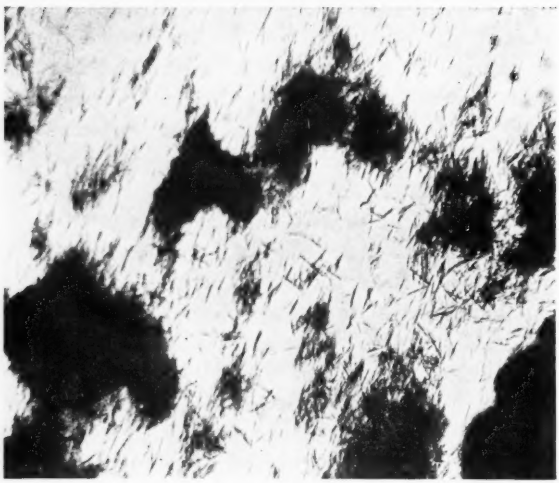

Fig. 71.—Sodium urate crystals obtained from a tophus (× 120).

time involving the right foot. Every year since then he had had a similar attack in one foot or the other until six years before admission, when the

attack occurred in both feet and lasted seven weeks. The feet were painfully swollen and there was slight fever. An attack four years before admission and one three years later involved also the left knee and right hand, respectively. Except for the last attack, after each one the pain disappeared and the function of the joint was restored. The last attack had left some pain in the feet. A diagnosis of acute recurring rheumatic fever had been made several times.

The patient showed questionably infected tonsils, moderate pyorrhea, and chronic prostatitis. The temperature of the left knee and foot was slightly elevated, but there was no limitation of motion and only a little swelling. The great toe, however, was moderately swollen. The heart, lungs, and abdomen were apparently normal. The absence of cardiac involvement made a reconsideration of the diagnosis of rheumatic fever imperative. After so many attacks of rheumatic fever cardiac disease practically always obviously exists. The acute recurring attacks of arthritis clearing up entirely, however, might certainly suggest rheumatic fever except for the normal heart. The urine showed albumin 2, the specific gravity was fixed around 1.012, and the blood urea was elevated to 66 mg. On account of the evident renal involvement gouty arthritis was suspected, and on closer observation three small tophi (Fig. 70) were found in the ear, from which sodium urate crystals were obtained (Fig. 71). The patient forgot to mention their appearance, but remembered that at the time of the "rheumatic fever attacks" he had been able to squeeze out chalky material. The blood uric acid was 6.1 and again 6.2 mg. The roentgenogram showed slight hypertrophic arthritis.

The diagnosis was chronic gouty arthritis. Low-protein (approximately 40 to 50 gm. daily) purin-free diet was given. The fluid intake was set at a high level on account of the fixed specific gravity of the urine and the elevated blood urea without edema. Atophan was administered and physiotherapy instituted for relief of pain.

Comment.—The absence of cardiac disease after so many attacks of supposed rheumatic fever made such a diagnosis untenable. Furthermore, in chronic infectious arthritis slight albuminuria is commonly present, but more than this rarely occurs. In a comparative analysis, by Nomland and Hench, of renal lesions associated with gout and chronic infectious arthritis it was found that except for albuminuria 1, with all tests of renal function normal, definite renal lesions occurred in only about 3 per cent of cases of chronic infectious arthritis, whereas in gout there were distinct types of renal disease present in 40 per cent of the cases. Osler discusses the types of nephritis associated with gout.

It is of clinical importance, therefore, to recall that if a patient with supposed chronic infectious arthritis presents dis-

tinct albuminuria with renal insufficiency gout should be suspected. In this patient, of course, the site of the arthritis, especially in the great toes, was very suggestive of a gouty type, and in all such instances blood uric acid should be measured and tophi searched for. Unfortunately, from the standpoint of diagnosis, even during the acute attacks, the blood uric acid may occasionally be normal. A history of recurring attacks of acute or subacute arthritis in a characteristic situation, the feet, and the presence of uricemia are important points for the diagnosis of gout. One tophus and the removal by a pinprick of chalky material showing sodium urate crystals clinches the diagnosis, even if the other points are lacking.

A discussion of the relationship of faulty purin metabolism to gout cannot be undertaken, but reference is made to Berglund.

The pathologic changes in gout consist of the deposition of sodium urate crystals about the joints, almost always in the fingers, toes, knees, and ankles, affecting first the cartilage, the capsule, and the periarticular structures. As the chronic irritation from the deposited uric acid continues, destruction of cartilage and hypertrophy and destruction of bone may occur, and the arthritic symptoms may then become chronic rather than recurringly acute. Surgical removal of these so-called tophi is disappointing; indeed the removal of the tophi entails the destruction of so much of the surrounding tissue and structures that it is scarcely ever advised. The best treatment is rest and hot dressings. When the toes and feet are affected the shoes may be modified so as to give the foot the correct balance. This is usually best done by means of a transverse bar and orthopedic heel. The transverse leather bar is applied to the sole of the shoe just behind the heads of the metatarsal bones. These transverse bars are crescent shaped to give support to the entire anterior portion of the foot. The orthopedic heel is the ordinary rubber heel made with an elongation on the inner side.

Case 4.—This obese patient, aged fifty, complained of pains in certain joints, especially the left knee. Otherwise there was nothing of note in her own or the family's history. About eight years before admission she began

to feel stiffness and pain in the knees. Her weight then was about 160 pounds. Oöphorectomy had just been performed and she was beginning to gain weight. Two years before admission her weight had increased to 200 pounds. The pain and stiffness spread to the ankles, and arch supports gave no relief. On the other hand, she could not walk without them. Baking the feet gave temporary relief. If she stayed off her feet the pain was con-

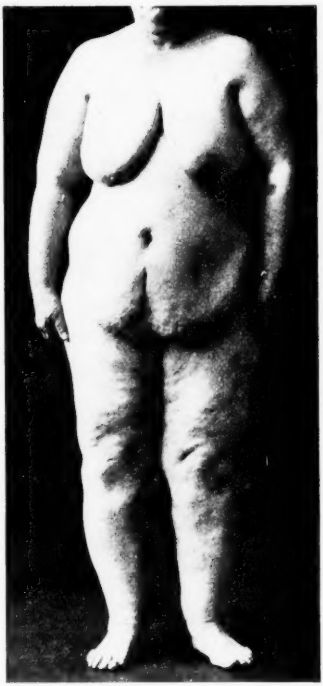

Fig. 72.—Obesity and pronated flat feet in a case of chronic traumatic (static) arthritis.

siderably easier. Walking caused pain under the anterior arches. She suffered from moderate dyspnea and palpitation.

There were many abscessed teeth and the tonsils were apparently infected. The weight was now 230 pounds. The heart, lungs, and abdomen were apparently normal. No joints were definitely swollen. The extremities showed variously local obesity, creaking, somewhat painful knees and flat feet (Fig. 72). The roentgenogram showed hypertrophic arthritis of the feet, ankles, and sacro-iliac joints.

The diagnosis was chronic traumatic (static) arthritis associated with obesity. A reduction diet of 1,000 calories was given. Orthopedic heels and transverse bars were applied to the shoes. Physiotherapy was instituted, and a wide abdominal supporting belt with a Cook shingle was provided. The modification of the shoes alleviated the pain in the feet almost completely.

Comment.—Acute or chronic trauma unassociated with infection will cause arthritis, generally showing the roentgenologic appearance of mild hypertrophy. Baseball fingers may be cited as an example. The prepatellar bursitis, seen most frequently in housemaids and nuns, is an example of chronic traumatic periarthritis. Obesity likewise is a definite cause of chronic traumatic arthritis, the so-called static form that affects those joints that carry the weight, namely, the lower lumbar spine, knees, and ankles. Flat feet soon result. A person seems to be able to carry, for a time at least, a considerable increase in weight, but eventually the penalty is generally an enlarged heart associated with increased blood pressure and static arthritis. Eradication of foci because of the arthritis is of little or no importance. Physiotherapy will provide a little temporary relief, but, unless the weight is sharply reduced and the excess trauma thereby removed, the arthritic pains will continue and increase with added weight. Dietary measures are, therefore, of prime importance. The patient must realize that a sky-scraper cannot be built on the foundation for a frame house without producing architectural defects.

In all types of chronic traumatic arthritis the elimination of the inciting trauma is the main point of attack. For the static type of chronic traumatic arthritis certain orthopedic measures are useful. As a rule, it is seen in persons who have suddenly put on excessive weight, subjecting their supporting structures to excessive strain. They complain of painful feet and legs and backache. The problem with the feet is again one of balance. The shoe must be modified so as to support the foot in the position that it normally assumes for bearing weight. This is best done by applying orthopedic heels with $\frac{1}{8}$ inch supination and distinct flaring of the heels on the inner side. The pain under the ball of the foot is almost always relieved by a crescent-shaped

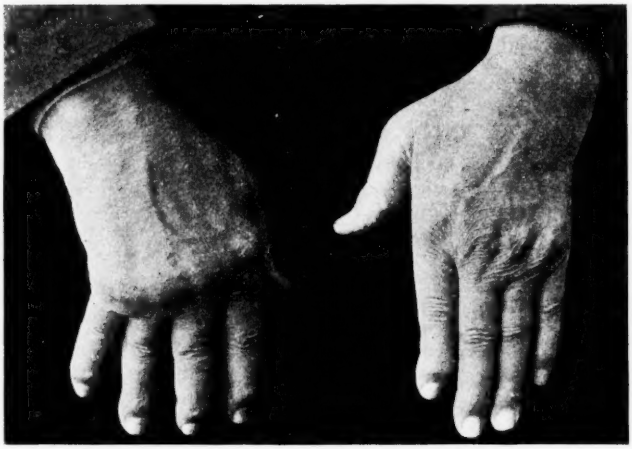

Fig. 73.—Residual chronic infectious arthritis in the hands. There was active mixed infectious and static arthritis in the lower extremities.

Fig. 74.—Destructive and hypertrophic bony changes.

transverse bar. For the backache, a wide canvas belt made to support the abdomen and to splint the back has been found to be beneficial.

In connection with chronic traumatic arthritis of the static form we recall another patient, who suffered from generalized arthritis of the typically infectious form ten years ago. It promptly became residual in the upper extremities (Fig. 73) with absolute cessation of pain and inflammatory activity, but remained active in the knees and ankles. When he was examined his weight was 271 pounds, a recent gain from 225 pounds. He had flat feet. The roentgenogram showed destructive arthritis in the hands (Fig. 74). Obviously, although the primary cause for chronic arthritis may, as in this case, be infection, if chronic trauma from obesity is superimposed on an already inflamed joint the latter will heal with difficulty if at all. The infected joints not thus subjected to trauma may heal promptly. Therefore, here also, although physiotherapy is essential, reduction in weight is of even greater importance.

Case 5.—This patient was a married woman, aged twenty-six, whose chief complaint was rheumatism. Ten months before admission, after an indefinite period of chronic fatigue, there was a sudden onset of subacute polyarthritis starting with swelling and pain in the right hand. Shortly afterward the knees and the other wrist became affected. The following month she contracted influenza and pneumonia. She was in bed two months and lost much strength and weight. During the febrile course, however, the joints improved somewhat. After convalescence the arthritis became worse, and the hips and back had recently been affected with stiffness and pain aggravated by damp weather. Treatment consisted of chiropractic adjustments, one course of hot baths, and tonsillectomy six months after the onset. The patient had been otherwise well aside from chronic constipation and occasional nocturia. She had been married three years and had had one miscarriage and one living child. One brother died from diabetes.

On examination the patient showed marked anemia and definite emaciation. The blood pressure was 95 systolic and 60 diastolic. Small epitrochlear and cervical lymph nodes were palpable. The kidneys were palpable, but the spleen was not felt. The hands, feet, ankles, and knees were swollen and there was marked muscle atrophy and pain on active and passive motion (Fig. 75). The fingers showed spindle-shaped swellings at the middle phalangeal joints with 50 per cent limitation of motion (Fig. 76). The roentgenogram is shown in Figure 77. The hands and feet were cold and clammy with at times a thin film of moisture, hyperhidrosis. There was considerable limitation of motion in the spine and wrists with flexion deformity of the elbows. The tonsils had been previously removed; the dental films were negative for abscessed or devitalized teeth, and the sinuses, gallbladder, appendix, and the pelvis were apparently normal. The Wassermann test was negative. The hemoglobin was 34 per cent, erythrocytes numbered

3,370,000, and leukocytes 15,100. The temperature was 99°, and the pulse rate varied from 80 to 100.

Fig. 75.—Swelling of the knees and atrophy of muscles in a case of chronic infectious arthritis.

The first two weeks in the hospital the temperature varied from normal to 1 degree above. Then, ushered in with a slight chill, there was a sharp

Fig. 76.—Spindle-shaped fingers in case shown in Figure 75.

febrile reaction for six days, the temperature going as high as 105° in the evening and dropping in the morning to normal. The lungs, heart, and urine

remained normal, but there was some soreness in the enlarged lymph nodes. The sputum showed no bacilli of tuberculosis, the blood smears no malarial parasites. The leukocytes remained between 11,000 and 12,000.

The diagnosis was chronic arthritis, etiologically of the infectious form, roentgenographically and anatomically of the periarticular form. The treatment consisted of baking and massage, and active and passive movements with instructions in carrying on these procedures as far as possible daily at home. Atophan was given for relief of pain. Cod-liver oil and a

Fig. 77.—Periarticular arthritis. There is very little bony change in the joint, but periosteal proliferation along the shafts near the joint. There is atrophy of cartilage of bone, and swelling of soft tissues.

high-calorie anticonstipation diet have been administered with extra portions of cooked liver as a hematonic. Another week has elapsed and the patient is ready for dismissal with definite (60 per cent) improvement in the joints, although the improvement was not accentuated by the febrile reaction.

Comment.—This patient represents the most important type of chronic arthritis, the so-called chronic nonspecific infectious arthritis or arthritis deformans. It is of the periarticular or

rheumatoid type. Chronic infectious arthritis may present changes in periarticular soft tissues, intra-articular synovial membrane or cartilage, or there may be hypertrophic or destructive changes in the bone. From the appearance of the joints themselves the presence or absence of bony changes cannot be always anticipated without the roentgen ray. There are certain important points to note: the tachycardia which was present even without fever, the cold, clammy hands and feet, the low blood pressure, the anemia, the loss of weight, and the prodromal period of unexplained fatigue.

SYMPTOMS OF CHRONIC INFECTIOUS ARTHRITIS

Chronic arthritis of the infectious type has not only more or less characteristic joint lesions, but is associated generally with some or all of several systemic disturbances. These may be: (1) Blood pressure below the expected tension, about 100 to 118 systolic or lower; (2) tachycardia without fever; (3) cold, clammy extremities with soft hyperhidrotic skin, which later may change to a dry, atrophic sclerodermatous form; (4) hypochlorhydria or achlorhydria; (5) lowered sugar tolerance; (6) secondary anemia, and (7) loss of weight and generalized weakness and fatigue. Just as in chronic glomerular nephritis or true Bright's disease, certain associated extrarenal findings (increased blood pressure, hypoplastic anemia, cardiac enlargement, and fundal changes) are of distinct importance in differentiating this form of renal disease from the other forms (focal nephritis, nephrosis, arteriosclerotic nephritis), so certain systemic manifestations are of importance in differentiating chronic arthritis of the infectious form from that not due to infection, but to trauma or to senescent retrogressive tissue changes. Their importance is, therefore, obvious. A recent summary (Hench) of about 300 cases of chronic infectious arthritis is summarized in the tabulation on page 582.

The interpretation of these findings is of decided interest. The tachycardia may be present with or without symptoms or other signs of cardiac insufficiency. Cardiac lesions associated with chronic infectious arthritis may be of four types: (1) the

TABULATION

SYSTEMIC MANIFESTATIONS OF CHRONIC INFECTIOUS ARTHRITIS

Tissue or function.	Abnormality observed.	Per cent.
Heart.....	Symptomless tachycardia without fever.	25
	Tachycardia with mild edema or dyspnea.	21
Blood pressure...	Below normal for all ages (Fisher's standard).	66
	Below 115 mm. mercury.	35
Blood.....	Anemia (in one as low as 28 per cent hemoglobin (Dare); erythrocytes 1,210,000).	30
Gastric acidity...	Achlorhydria.	28
	Hypochlorhydria.	19
Glucose tolerance.	Reduced.	65
Kidney.....	Albuminuria, mild grade only; other renal functional tests practically always negative.	90

most common is a simple tachycardia, perhaps toxic, which fluctuates considerably; (2) there may be persistent prolonged tachycardia suggestive of actual myocarditis, the cardiac musculature partaking of the same inflammatory involvement as the skeletal musculature (focal myocarditis has been observed by us occasionally at necropsy on such patients); (3) pericarditis is an occasional complication, and (4) endocarditis may occur especially in the younger patients with chronic infectious arthritis; the presence of definite endocarditis, however, should make one suspect and rule out rheumatic fever before a final diagnosis of infectious arthritis is made.

The lowered blood pressure associated with the cold, clammy extremities and the sluggish capillary stream that may be observed by the Lombard method is indicative of depression of vasomotor tone. The quite consistent presence of some or all of these phenomena in arthritis of the infectious form is in sharp

contrast to their general absence in chronic arthritis of the other etiologic types. It might be mentioned parenthetically that the low blood pressure which, as shown by our series and by actuarial tables, is more or less the rule in cases of chronic arthritis and duodenal ulcer (two outstanding examples of disease accepted as being causally associated with focal infection) might suggest the need of a revision of the wide-spread opinion regarding the need for eradication of foci in cases of hypertension. Their eradication would seem to be more generally indicated in cases of hypotension than of hypertension. A period of prodromal fatigue is common. A patient, therefore, newly experiencing unexplained chronic fatigue associated with lowered blood pressure and clammy hands may deserve special attention to foci of infection in view of the possibility of incipient chronic arthritis. These may be important manifestations of the need for special prophylactic care.

General depression of secretory activity would seem to be reflected by the high incidence of achlorhydria or hypochlorhydria and lowered tolerance for sugar. Regarding renal function, although mild albuminuria is to be expected, a greater degree than this is quite rare, and usually explained by the finding of an independent renal lesion or the discovery that the arthritis is of a gouty type, as was previously discussed. A common fallacy is to expect the appearance of chronic Bright's disease which, in our experience, occurs extremely rarely in cases of chronic infectious arthritis.[7] Many of these systemic physiologic aberrations are best explained on the basis of chronic toxemia associated with infectious arthritis rather than by assuming metastatic infection in all these areas.

Just as there are diffuse systemic changes in chronic infectious arthritis so is there generally diffuse involvement of joints, and the fundamentally systemic nature of arthritis of the infectious type is further indicated by its progressively polyarticular distribution. In other etiologic forms of arthritis, such as the traumatic (static) and senescent, the joints affected are fewer, more localized to the areas exposed to trauma, and not markedly polyarticular.

TREATMENT OF CHRONIC INFECTIOUS ARTHRITIS

When a diagnosis of arthritis of the infectious type has been made radical treatment is automatically indicated. Arthritis is so prone to cripple progressively and to cause increasing mental and physical suffering and financial dependency, that in its malignancy, at least as far as health and happiness are concerned, it may well be compared to cancer. Just as it is the invariable principle in cancer to remove not only the primary neoplastic focus but its metastatic foci, even though only presupposed to exist in adjacent lymphatic structures, so in infectious arthritis a principle hardly less variable must be adopted in similar order, namely, to bend every effort not only to the removal of the primary foci, infected teeth, tonsils, and so forth, but also to the suppression of the metastatic infection, the joint inflammation. This demands a policy of irradicating all foci, with the patient's entire knowledge of the uncertainty of condemning certain foci and with his willingness to coöperate in the removal of foci "on suspicion" in keeping with such a program.

Irradication of foci.—The foci most often found are in the tonsils and teeth. Devitalized, as well as abscessed teeth, must be extracted. Recent dental bacteriology indicates that the greater percentage of devitalized teeth soon become, or already are, infected, even though a tissue reaction is not apparent in the roentgenogram.[10, 12] Pyorrhea may be just as important to eliminate as a possible cause, and is vigorously treated. It is not always possible on inspection to prove a tonsil diseased. Many tonsils removed simply on suspicion, when there is no history of tonsillar infection, have proved to be markedly infected. C. H. Mayo has often pointed out that the small atrophic tonsil that has lost its power to react and localize its infection may be more dangerous than the large hyperemic tonsil. It is far better to remove on suspicion a tonsil that may turn out to be innocent than to ignore a small tonsil that frequently proves on microscopic section and experimental inoculation to be capable of producing arthritis.

The sinuses do not often seem to be a focus for arthritis. The lungs probably never harbor the infection that causes the

common type of arthritis, although a particular type of arthritis, pulmonary osteo-arthropathy, is not uncommon. Adequate proof of etiologic relationship with colonic stasis, visceroptosis, chronic constipation, autointoxication, and so forth, is wanting. The rôle of corrective diets will be discussed. Infection in the intestinal culdesacs, the appendix and gallbladder, is not often the apparent cause of arthritis and may well be not the father of the joint lesion but its brother, born of a common primary focus. If definite inflammation exists in the gallbladder or appendix, the organ should be removed to reëstablish the body physiologically as much as possible.

Latent infection in the prostate may be uncovered by the method used by von Lackum, and seems to be a definite cause in certain cases. Pelvic infections may constitute a primary focus, though not often. Moench and Walters have discussed the relationship of cervical infection to the production of chronic arthritis. In many women there is an exacerbation of the arthritis just before or during the menses, which might suggest intrapelvic focal infection. From the investigations of Hunt and Hench it would seem that such menstrual exaggerations of arthritis do not reflect pelvic infection, but are merely the result of cyclic variations in the metabolic state, only one of the physiologic manifestations attendant on the menses and often present without clinical or bacteriologic evidence of definite infection.

A policy of eradicating foci is demanded for chronic infectious arthritis, for it is rarely possible to name with certainty the individual activating focus. It must also be remembered that a chronic dormant focus may be allowed to act if the patient's resistance is suddenly altered, for instance, by an independent infectious disease like influenza or by exposure to cold. In such a case the focus is the same; it is the patient that changes. Whether an acute exogenous focus ever exists is uncertain, although the entire absence of any foci at the onset of an occasional arthritis may lend credence to the patient's belief that he "must have swallowed the germs one day."

Unwarranted disappointment is often expressed at the results obtained from eradication of foci. The need for eradication is

just as urgent, but high expectations should be modified for obvious reasons. To revert to the analogy before used, were a main cancerous growth removed with little or no attention to eradication of adjacent lymphatics, failure would be almost invariable. Many patients with chronic arthritis spend years of valuable time hunting for the cause, searching for further foci to eradicate, with an absurdly minimal care of the infected joints themselves, not realizing that one joint with a well developed inflammatory process may, as far as we know, act as a focus even more persistently and menacingly than, for instance, an original oral focus. Therefore, failure must and does surely result in a large percentage of cases when the physician or patient is content with eradication of foci and analgesic medicines as the sum total of treatment.

Physiotherapy.—For the suppression, localization, and possible termination of the metastatic infection in chronic arthritis, that is, the joint lesions, physiotherapy in some form is absolutely essential. But such treatment to be successful must be just as persistent and progressive as the disease itself. Hence, the significance of the usual failures resulting from "three-week courses" at springs, baths, and so forth. The objective and subjective discomfort in the joint almost invariably recurs, and the physiotherapy, no matter how adequate and scientific during its application, receives the onus of the failure. In analyzing the reasons for failure in the previous management of cases of chronic infectious arthritis we have come to the conclusion that, although it is regretfully admitted that treatment for this malady is inadequate and nonspecific, failure too frequently results, not from the inadequacy of available beneficial measures themselves, but from the inadequacy and haphazard way of applying such treatment as is available. Therefore physiotherapy, along with other useful measures, to be successful must be faithfully and persistently carried out with the chronicity of the malady kept in mind. The psychology of the patient with arthritis will not allow the continued expenditure of much money for physiotherapeutic or electrotherapeutic measures that obviously result in only slow improvement, or if received in short "courses" are

followed by only temporary benefits. No matter how much relief a mineral bath, a diathermic treatment, or one massage at the hands of a professional will give, the patients will not long continue to sacrifice so much of their time, convenience, and money. Hence the great importance and utter necessity of instructing the patient to carry on his own physiotherapy in his own home daily, with his own simple, inexpensive apparatus. Only when the inconvenience of appointments and the apparently interminable financial outlay attendant on long-continued professional physiotherapy are so obviated or minimized, will the patient willingly adopt a progressive and faithfully persistent plan of treatment.

The principles of physiotherapy are simple and seem too trite for discussion. Briefly, however, all such measures, whether they consist of massage, active or passive motions, or heat by means of the sun, hot water bottles, electric pad, baking machine. diathermy, hot bath, or mud bath, are to accomplish one thing only, the increased flow of fresh blood to the infected tissues by local vasodilatation and increased pulse beat with the resultant enhanced removal of toxins and débris of infection. It is doubtful whether diathermy or other of the more expensive measures requiring elaborate apparatus produce sufficiently better results consistently in chronic arthritis (not acute) to warrant their prolongation to the exclusion of instruction and use of the simple methods applicable to home use. On the other hand, however, the value of a preliminary period of intensively applied professional physiotherapy is great, and such a period is generally necessary to give the patient a good start. Especially is this true when active motion is markedly restricted in range, and passive motion is essential to restore joint function.

Furthermore, as an occasional and systematically applied supplement to the patient's own efforts, such intermittent professional attention is necessary and valuable as a control and stimulus. But, even though the patient's own physiotherapy is amateurish and efficient only to a minor degree, the sum total of the benefits received from his own persistent efforts is generally far greater than the brief and passing course of professional at-

tention which usually leaves the patient high and dry in his ignorance of how to maintain the benefits received therefrom.

The busy general practitioner usually has neither the time nor training to instruct patients adequately in such home physiotherapy. If, however, such instruction is not given under the supervision and direction of the physician, his patient will almost invariably soon get such help as he can from the chiropractor and osteopath. Approximately, 75 per cent of a group of patients questioned had resorted to such methods in desperation as against 46 per cent of patients generally. The usual reason given (even by the most intelligent patients, which included one college president) was that all the various physicians did was to remove a focus or two and give medicines, none of which gave the directly demonstrable relief which often attended the very first "laying on of hands," outside of the medical profession.

In most communities there is available a graduate physiotherapist who will coöperate with the physician in the care of patients with arthritis. The details of technic and instructions should be left entirely to the physiotherapist. The activity of such treatment, the time for intensive application, the regulation of the schedule for home physiotherapy, and the appraisal of results are the physician's task. At the Mayo Clinic the instrument of choice is a cradle of carbon lights, a baking machine, which for convenience varies in size according to the areas to be treated, and which may be purchased from local tinsmiths at a moderate cost (approximately ten or fifteen dollars). The use of such an instrument, always followed by active selective exercises and when possible by massage by a relative, will by its availability in the patient's own home and by the inexpensiveness of the apparatus promote a plan of prolonged progressive physiotherapy. A large percentage of the arthritic deformities are absolutely preventable by means of adequate physiotherapy and orthopedic measures, and are too often the stamp, not of the severity of the disease, but of the inadequacy of the patient's persistence or the physician's attentions.

During the acute stage of the process motion must be entirely restricted or markedly limited to allow the infection to localize. When the subacute stage is reached (as shown by diminution of fever if the process has been acute, the willingness of the patient to try at least to move the joint, and the diminution of the intensity of the local redness, swelling, and pain) then local heat must at once be supplemented by motion, passive at first, active as soon as possible. The activity of physiotherapy is more or less in reverse ratio to the activity of the disease. In spite of pain alone the patient must be encouraged to restore active motion. If a reaction consisting not only of pain but also of redness and swelling occurs, temporary diminution in the activity of the physiotherapy is necessary. To prevent deformity, however, it is imperative that the activity of the physiotherapy lag not far behind the subsidence of the arthritic activity.

Contrast baths, as described for senescent arthritis, are easily carried out and very useful when the extremities are involved.

So often patients come to us after the deformity has taken place, usually in the form of a flexion deformity, with the expectation that the orthopedist will be able to correct the deformity at once and restore perfect function. If there could be closer coöperation between the physician and the orthopedic surgeon when the arthritis is in its acute state and deformities can be easily prevented, much less would be required to correct so many severe deformities. Usually the patients are allowed to assume the position of greatest comfort, which is flexion. In the knees the production of flexion deformities is often aided by prolonged support with pillows. Generally the physician alone attends the patient with acute and early chronic arthritis, while the orthopedist's visit usually predicates deformities, often preventable in whole or in part.

We have found that the best way to correct all but the slightest flexion deformities of the knees is to apply a plaster-of-Paris cast, making the plaster heavier in the region of the popliteal space. When the cast has sufficiently dried, usually twenty-four to forty-eight hours later, the plaster is cut through behind the knee and a spreading device inserted.[4] This device is so

made that the leg may be gradually straightened from day to day and can be manipulated by the patient himself. Casts must not be left on long, not more than about ten or fourteen days, or resulting limitation of motion may be great. This type of cast may be used during the entire process of straightening the leg, and the application and reapplication of casts be avoided during the patient's stay in the hospital. When the leg has become entirely straight another cast is applied with the leg in full extension, and is later cut into a half cast, which is worn while the patient is in bed and at night. During the day a stiff-legged brace is applied, holding the leg in the corrected position and making it possible for the patient to be up and around. If there is any flexion deformity left following the corrective casts, the pain usually makes it impossible for the patient to walk with any degree of comfort, therefore great care should be taken to obtain complete extension of the leg. For the correction of flexion deformities of slight degree only, physiotherapy with Buck's extension alone may be successful. For those of greater degree the corrective cast reduces the time and expense of hospital care more than Buck's extension apparatus.

For flexion deformities in the elbow and fingers manipulation under an anesthetic is usually the best method of beginning the corrective procedure. Following this a plaster-of-Paris extension splint is usually applied to the arm, so made that greater extension can be applied from time to time. In this way almost complete correction is eventually secured. As an adjunct to this we find it beneficial to give diathermy and the pulsating direct current, known as sinusoidal, and then follow this with massage. This stimulates the extensor muscles to function better and further tends to correct the deformity. The deformities seen in the hands and fingers are indeed discouraging. Manipulation under an anesthetic and placing the fingers in the optimal position seems to be the best way to overcome them. Following this, diathermy, sinusoidal current, and massage must be used and may be beneficial. Instruction is given the patient in the application of baking and massage, as it is impossible for him to carry out diathermy and sinusoidal treatment after leaving the hos-

pital. However, a preliminary course of treatment with electrotherapy and following this with heat, by means of a baking machine, and massage, as a rule, gives the maximal benefit.

In cases of spondylitis deformans with flexion deformity, especially in young adults, diathermy given for four or five days, followed by the pulsating sinusoidal current and massage together with corrective exercises and occupational therapy, will often materially correct the deformity, ease the pain, and fit the patient for his regular duties better than any other form of treatment. This course of treatment usually takes from three to four weeks. Instruction is then given in the application of heat and massage, a steel back-brace is provided, and certain corrective exercises, including deep breathing, that can be carried on at home are outlined.

Occupational therapy.—Occupational therapy is very desirable if it can be obtained. Hospitals maintaining such departments have a fortunate therapeutic auxiliary to provide active motion by means of interesting work, such as basket-weaving, the use of the loom, and knitting, as well as other methods such as the rowing machine, which more properly comes under the department of physiotherapy.

Climate.—The ability of the patient to forecast weather changes by variations in his pains shows that variations in climate affect chronic arthritis. In general, cold climates are not well tolerated and a warm dry climate is best. Although warm climates may make patients feel better they do not often cure the disease. Furthermore, climatic conditions are not a direct but a predisposing cause of arthritis, as it will be recalled that the earliest record of arthritis is found extensively in the mummies of Nubian and other Egyptian peoples where the climate is never rigorous. When other measures fail, and if the patient is financially able, a prolonged stay in a warm climate may help check the disease.

Medicine.—There is no adequate medicine for chronic infectious arthritis. The specificity and analgesic properties of salicylates that is so noteworthy in cases of rheumatic fever is only slightly manifested in chronic infectious arthritis. Anal-

gesics, such as acetylsalicylic acid, salicylates, atophan, and pyramidon are permissible and desirable, for if relief from pain is thus obtained more active and passive motion can be carried out. Medicine, however, is only a means to an end, and failure should be anticipated by the physician whose armamentarium includes medicine as the only supplement to suppression of foci. Certain drugs are here used empirically, Fowler's solution to tolerance, alternating with tincture of iodin, or the iodids to tolerance, with intervening periods of a week or two without medicine. When anemia is present the customary inorganic hematonics may be used, but should be combined with organic iron-containing substances, notably the diets containing much liver recently advocated. One hundred grams of cooked liver daily are useful and well tolerated by most patients . When achlorhydria is present, one to two drams of dilute hydrochloric acid in fruit juice should be sipped during each meal.

Vaccines.—In our experience specific vaccines are of little benefit. The various protein and other foreign substances (mercurochrome, sulphur compounds, milk preparations) seem to bring results only as they produce a reaction in the defensive mechanism of the body accompanied by chill, fever, and sometimes gastric upset. Such preparations, if given intramuscularly or intravenously in doses insufficient to produce such a reaction, rarely seem directly responsible for any benefit. Vaccines seem at times entirely useless, but in other cases produce markedly beneficial results. They are not indicated in all the milder cases. We prefer typhoid vaccine (*Bacterium typhosum* and *Bacteria paratyphosa A* and *B*) intravenously and use triple typhoid vaccine as follows: For greater convenience in measurement the vaccine is mixed with sterile water or normal sterile physiologic salt solution so that 1 c.c. of the water or salt solution contains 50,000,000 bacilli. A fraction of a cubic centimeter of this mixture may thus be measured to give the desired dose. The initial dose intravenously is from 10,000,000 to 15,000,000 bacilli. The dose is increased to 25,000,000 to 50,000,000 and to 75,000,000, if necessary more, to obtain each time a reaction consisting of a chill and a rise in temperature to 102° or 103°. Occasionally

nausea and vomiting occur. The injections are given every fourth to seventh day in a series of from four to seven injections, after which they are omitted for from four to eight weeks. Frequently relief is not obtained by the first injection; the course is continued, however. If relief in the way of decrease of pain, stiffness, or swelling is obtained after each injection they are continued until no such relief follows. If the patient, however, seems to have more soreness or stiffness after the injection, the dose is definitely decreased, as sensitization is apparent.

Diet.—Manifold diets are in vogue, some based on sound principles, others merely fads. The low carbohydrate diet has not seemed beneficial here, in spite of the comprehensive and thorough observations of Pemberton and the apparent soundness of his theories. Low protein diets are a heritage from the time when arthritis was compared with gout and purin disturbances. It is true that unbalanced diets with a preponderance of sugars in one case, or of meats in another, are often attended by increased pain and stiffness of the joints. We, however, advocate a high-calorie, anticonstipation diet for the thin emaciated patient who has obviously lost much muscle tissue, general weight and strength, and who needs plenty of good nourishing food; and we prescribe a weight-reduction diet for the obese patient who has the element of chronic trauma added to the infected joint.

The causal relationship between constipation and arthritis cannot be fully discussed here. At times it seems distinct, but sufficient scientific proof is lacking. Constipation often seems, however, to be a very definite aggravating factor, and it should be controlled by a diet containing from six to eight helpings of vegetables and fruits daily with a liberal intake of fluid, supplemented, if necessary, by bran, mineral oil, or agar-agar.

General hygienic care must be adopted to restore and reenforce bodily resistance. Such infections as chronic arthritis do not probably only come because the specific organism enters the body, but because the soil, the individual patient's body, always was or has become favorable for the growth of such organisms. A great many people with chronic infected tonsils

and very bad teeth never contract arthritis because their general resistance is kept high. This is accomplished by regular habits of sleep, exercise, and work, plenty of sunshine, fresh air, and abundant nourishing food. The building up of one's resistance may occasionally alone stop the disease. It should be recalled that for tuberculosis medical science has no specific cure, although thousands of lives are being saved by teaching such patients to develop their resistance and stop the infection indirectly. Similar care is essential in chronic infectious arthritis.

Education.—The education of the patient concerning the nature of his malady is of utmost importance to a satisfactory result. A full and frank discussion of the possibilities and limits of medical aid will obtain his confidence and elicit his fullest coöperation in the fight against his disease. The instruction in physiotherapy is given daily to the patients in the Clinic or on the hospital service. Two weekly seminars on the care and treatment of arthritis are given for patients and their attendant relatives, to obtain proper home morale and encouragement. Certainly such a program of education is just as necessary in chronic arthritis as it is in diabetes or nephritis, for in this struggle against arthritis, as in these other chronic diseases, the patient himself must be the "player," the physician merely the "coach."

In spite of attendance on many physicians and spas, the average patient knows practically nothing about his condition except that the disease bears the name arthritis. The physician must discuss, consecutively and simply, the physiology of the joint, the source of the infection, the need for eradication of foci, and the results that may or may not be expected from it, the reasons for special diet, the rationale of physiotherapy and the necessity for persisting with it, and the efficacy of medicines. Not only must he courageously emphasize his own views on these questions, while realizing the value of the differing opinions of others and the deplorable lack of knowledge concerning the cause and cure of arthritis, but he must explain away the fallacies and fancies that make up "rheumatic lore." Public instruction has given a fundamental background of knowledge to the sufferer

with tuberculosis and cancer. Such instruction is lacking for the victim of arthritis, and has been left almost entirely to the cultist and the newspaper advertisements. The proper presentation of such knowledge is one of the first steps toward the solution of the great economic problem of this crippled multitude.

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POSTTYPHOID CHONDRITIS AND OSTEOMYELITIS

WILL T. FITTS AND HOWARD R. HARTMAN

A man, aged forty-two, was examined at the Clinic May 24, 1926, at which time he complained of a tender enlargement just mesial to the left nipple and a small discharging ulcer a few inches above it. He had been well and strong until December, 1925, when for a week he was constipated and experienced pronounced lassitude. Then followed a week of general aching, with particularly severe headaches, occasional nosebleed and slight fever, and three weeks of unconsciousness accompanied by high continued fever. After this his convalescence was rapid mentally, but slow physically. The illness was diagnosed influenza by the attending physicians.

During the first week of convalescence the patient noticed localized tenderness below and to the right of the left nipple, which gradually spread to the left anterior aspect of the chest and the axilla. There was considerable pain which was aggravated by respiration, and soon a tender, painful swelling about 10 by 10 by 8 cm. appeared in the inner portion of the left pectoral muscles that interfered with the use of the arm. Whether or not there was fever at this period was not ascertainable from the patient. February 12, 1926, the mass, with part of the adjacent pectoral muscles, was removed, and pronounced "melanotic sarcoma" by the examining pathologist, although the surgeon did not concur in this opinion. The inner angle of the operative incision broke down more than once just as healing was almost complete. The tender swelling just below and inside the left nipple had subsided and reappeared several times since its onset. In the interval between the patient's operation and his admission to the Clinic he received fourteen roentgen-ray treatments to the left upper anterior surface of the chest and axilla. Four years before he had sustained a crushing injury to the chest and several of the left ribs were broken near their anterior extremities. He had been shot in the face and chest by a shotgun several years before, and most of the shot still remained in his body. A few weeks prior to the beginning of his present illness he had spent a short time with a brother-in-law who was suffering from typhoid fever.

The patient was pale and appeared ill, but nothing of special importance was found in the general physical examination other than the local condition of the chest, which consisted of a reddened, tender swelling in the region of the sixth costal cartilage and a small discharging sinus at the fourth costosternal juncture. There was moderate secondary anemia with essentially a normal number of blood cells, the blood Wassermann test was negative, and the urine was normal. There was no fever. Roentgenograms of the chest

showed some evidence of a destructive process in the anterior ends of the fourth, sixth, and seventh ribs, and their corresponding cartilages. Roentgenograms also showed several small foreign bodies, presumably shot, in the chest wall, but none was adjacent to the anterior portions of the left ribs. The blood gave a positive Widal test, and culture of the seropurulent material from the sinus on the wall of the chest showed a luxuriant growth of *Bacillus typhi*. None was found in the cultures made from urine, feces, and bile aspirated by a duodenal tube. A diagnosis of posttyphoidal osteomyelitis of the ribs was made and operation advised. This was postponed temporarily because of an exacerbation of the inflammation at the site of the original process. However, it subsided and, June 7, Dr. Harrington explored the sinus which was found to lead to the left fourth costochondral juncture. The inner portion of the cartilage had been destroyed for about 2.5 cm., as had also about 5 cm. of the adjacent rib. The affected area was filled with foul granulation tissue; all of this was removed. The pathologist reported "chronic inflammation with areas of foreign-body giant cells." July 6 an abscess at the sixth left costal cartilage was drained, the pus on culture showing *Bacillus typhi*. A week later minor thoracectomy was performed, the inner anterior ends of the sixth and seventh ribs and their cartilages being removed because of the chondritis and osteomyelitis. The pathologic report on this tissue was the same as that on the material removed previously.

August 28, the original sinus was completely healed and the wound of the last operation was practically healed, there being only a small area of granulation tissue and very little discharge. The patient was in splendid physical condition, feeling strong and well, had gained 15 pounds in weight, and was about to be dismissed from observation. He had received no medicinal or vaccine treatment, but had had Alpine lamp and direct sun-ray exposures to the granulating surfaces.

Comment.—It is interesting to speculate on the character of the mass removed at operation prior to the patient's coming to the Clinic. It did not contain pus, so the patient was told, and had a dark bruised appearance. It may be assumed, however, that the condition was hemorrhagic myositis followed by organization of tissue. Nothing suspicious of malignancy could be found from which the pectoral mass removed elsewhere could have metastasized. Whether or not the old injury to the chest played a part can only be conjectured. However, it is worthy of consideration.

Posttyphoidal complications in bones are relatively uncommon. Only two previous cases have been observed at the Mayo Clinic. One case, typhoid of the spine, was observed several years ago; the other, reported by Lyons in the Clinic Bulletin in 1924, was typhoid osteomyelitis of the ribs, of one year's dura-

tion. Its presence was first manifested one year following typhoid fever. The disease was cured surgically.

The disease has been recognized for almost a century, but its true nature has been largely determined since Eberth's discovery of the *Bacillus typhi* in 1880. A comprehensive treatment of the subject is to be found in Keen's "Surgical Complications and Sequels of Typhoid Fever."

The direct cause is the *Bacillus typhi*, but predisposing causes are trauma, such as blows to bones or strains on muscles at their attachments, and poor general health with accompanying lowered resistance. Linberg reports a general spread of typhoid fever throughout Russia from 1919 to 1923, which was attended by an unusual number of cases of typhoidal chondritis. He attributes this, in large measure, to the serious economic condition of the country at this time. Other observers have attributed a predisposing influence to scorbutus. As is well known, bacteriemia occurs early in the course of typhoid and thus affords an opportunity for a general distribution of the organisms. Their presence in the spleen and bone marrow years after the patients recover from the illness could explain the late bone complications. Keen believes that the remarkably rapid growth of certain youths following attacks of typhoid may be due to the irritating presence of the bacilli in the osteogenetic tissue. Occasionally, the bacteriemia in typhoid occurs late rather than early. If one assumes the presence of agglutinins in the blood at this period, clumps of bacilli thus formed could lodge in the various terminal blood vessels and produce lesions of bone as well as those of the circulatory system. The pathologic changes are not distinctive; they were discussed in detail recently by Linberg.

Chondritis shows a marked tendency to spread to the adjacent cartilages, and multiple fistulas usually develop. The symptoms likewise are not characteristic. There is usually thoracic pain, especially when the patient breathes or moves. Osler says the most striking features are chronicity, indolence, and a tendency to recurrence. The diagnosis rests finally on the presence of *Bacillus typhi* in the area of destruction of tissue.

The treatment is largely surgical and entails complete removal of the diseased tissue. Vaccine has its advocates, but it does not seem to be based on sound scientific principles. As was suggested by Ferrari, it does not seem reasonable that the immunity already produced by a patient suffering and recovering from a typhoid infection could be augmented by the administration of typhoid vaccine. This author emphasizes also the efficacy of absolute and prolonged rest. There may be some justification for the belief held by some observers that in typhoid infections of the bone complicated by the secondary invasion of other pyogenic bacteria, such as staphylococci and streptococci, an autogenous vaccine produces good results.

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INFARCTION OF THE INTERVENTRICULAR SEPTUM WITH COMPLETE HEART-BLOCK AND STOKES-ADAMS' SEIZURES

FREDRICK A. WILLIUS

CASES OBSERVED IN THE MAYO CLINIC

Case 1.—The first patient was a man, aged sixty-five, who had been under our observation intermittently for ten years. During most of this time the systolic blood pressure was usually less than 200 and the diastolic from 100 to 120. Four years previously he had suffered from a cerebral hemorrhage with resulting hemiplegia, from which he practically recovered, and he returned to a fairly active business life.

On the last day the patient was observed in the Clinic he was seized with severe midretrosternal pain after partaking of an unusually heavy evening meal. The pain, which varied in intensity, radiated over the left anterior aspect of the chest corresponding to an area the size of the palm of the hand. The facies was ashen, cold perspiration covered the body, and there was every evidence of excruciating pain. The patient was attended at his home, and special laboratory examinations were therefore not available.

Examination revealed marked pulmonary emphysema and numerous coarse râles throughout the chest, the result of chronic asthmatic bronchitis. It was impossible to outline the cardiac borders definitely owing to the hyperresonant percussion note, but previous examinations had revealed moderate cardiac hypertrophy coincident to the hypertension. The heart tones were somewhat rapid, distant, and of poor quality, and the accentuation of the aortic second tone which had been noted previously was absent. A diagnosis was made of acute coronary obstruction with myocardial infarction. Nitroglycerin and morphin were administered, but afforded only partial relief.

Fifty-three hours after the onset of the attack I was hurriedly summoned by the patient's wife, who thought that he was dying. When I arrived, a few minutes later, the patient was having repeated opisthotonic convulsions with complete loss of consciousness. During the convulsions the radial pulse was absent and the heart tones imperceptible. As the convulsion wore off and consciousness returned, the radial pulse again became perceptible, about 30 beats each minute. This was soon followed by regular tachycardia, the rate varying from 90 to 110. The convulsions lasted about a minute, and the periods of freedom varied from two to ten minutes. Approximately thirty convulsions occurred in three hours and fifteen minutes, when death ensued.

Necropsy.—The heart weighed 409 gm. The descending branch of the left coronary artery was completely occluded by a thrombus, beginning at a

point 4 cm. from the aortic orifice and extending peripherally. There was moderate sclerosis of the right coronary artery. A large infarction involved a considerable part of the interventricular septum (Fig. 78). There was slight calcification of the aortic cusps. Histologic study of the muscle of the heart showed a definite increase in the interstitial connective tissue. The muscle fibers appeared fragmented in some areas, and there were also slight fatty changes. The only other significant changes were generalized arteriosclerosis and a small aneurysm of the basilar artery.

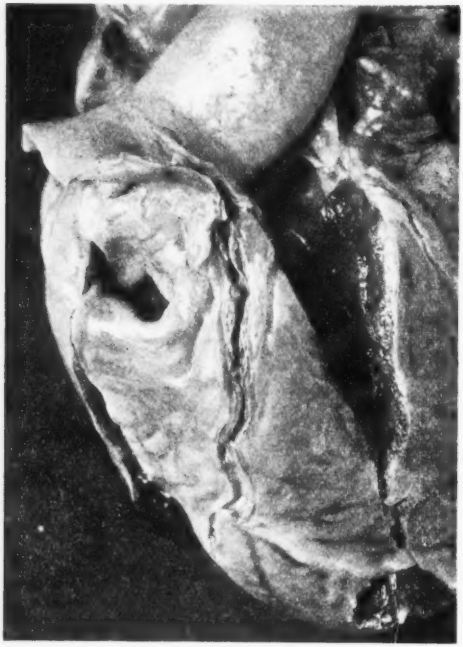

Fig. 78.—Occluded coronary artery opened and ventricle incised to show the extensive infarction.

Case 2.—The second patient was a man, aged forty-seven, who had apparently been in reasonably good health. While driving his automobile and becoming quite excited under the stress of traffic he suddenly felt excruciating retrosternal pain which radiated into the left arm. There was no preceding history of anginal attacks. He was seen about two hours after the onset of the attack. The chest was so deformed that it was impossible to outline the cardiac dulness definitely, but it was apparently not increased. The tones were rapid, distant, and of poor quality. The facies was ashen,

the brow covered with beads of cold perspiration, and the whole appearance indicated great suffering. A moderate degree of peripheral arteriosclerosis was present. The examination otherwise was essentially negative. The pain was only partially relieved by the administration of morphin and nitroglycerin. No special laboratory examinations were available since the patient was attended in his own home. The diagnosis was made of acute coronary obstruction with myocardial infarction. Thirty-one hours after the onset of the attack the patient was seized with opisthotonic convulsions, and lost consciousness. The convulsions continued at irregular intervals and were almost identical in detail with those described in the first case. The pulse between the attacks was perfectly regular and the rate varied between 80 and 96. It dropped suddenly to 28 or 30. Then the radial pulse and heart tones became imperceptible and the convulsion immediately began, and lasted about a minute. The patient suffered about twenty convulsions until his death, ten hours later. No pathologic data were available in this case, as necropsy was not permitted.

DISCUSSION

A great deal has been written during the last few years concerning infarction of the myocardium, indicating that a hitherto obscure clinical syndrome usually discovered by the pathologist has been elaborated into a clear-cut clinical entity. Krumbhaar and Crowell, in a recent review of 654 cases of spontaneous rupture of the heart, which they conclude is usually the result of infarction, found the interventricular septum to be affected in less than fifteen cases. No mention was made of whether or not complete heart-block and the Stokes-Adams phenomena were present. Jellick, Cooper and Ophuls, in 1906, and MacCallum, in 1908, reported cases of infarction affecting the auriculoventricular bundle, with Stokes-Adams' seizures. Wearn, in reporting nineteen cases of myocardial infarction, mentioned two cases exhibiting complete heart-block, but did not mention the related clinical syndrome.

Two cases are reported of acute coronary obstruction with myocardial infarction causing complete heart-block and Stokes-Adams' seizures. This clinical picture is apparently rare and has occurred only twice in our experience at the Mayo Clinic. It is a regrettable fact that we were not able to obtain electrocardiographic studies in these cases, as they would undoubtedly have been interesting.

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THE USE OF DIURETICS IN CARDIAC EDEMA

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One of the most distressing symptoms in severe cardiac disease is massive edema. Digitalis and caffein have often been valuable in bringing about reduction of the edema by diuresis, yet certain resistant cases are met with which fail to respond. In such cases beneficial results have been obtained by the use of certain organic mercuric compounds and acid-producing salts. Saxl and Heilig, in 1920, were the first to show the diuretic possibilities of organic mercury compounds. Schultz, in 1918, reported good results following the use of calcium chlorid in war nephritis with edema. Other authors have similarly employed calcium chlorid, ammonium sulphate, and ammonium chlorid in cases of cardiac and nephritic dropsy. We have recently found that the combined use of an acid-producing salt and certain organic mercuric compounds bring about more definite results. Some acid-producing salts are disagreeable and difficult for the patient to take. Of these, ammonium nitrate has been found to be less disturbing, and detailed studies have shown it to be nontoxic. In the cases reported here ammonium chlorid and merbaphen[1] were used in Case 1, and ammonium nitrate and merbaphen in Cases 2 and 3.

REPORT OF CASES

Case 1.—A man, aged sixty-three, entered the Clinic January 20, 1925, complaining of swelling of the entire body, which had begun two years previously. In November, 1923 the edema of the ankles and legs became more marked and this was followed by a gradual swelling of the abdomen. Abdominal paracentesis was performed eight times, and from 8 to 11 liters of fluid were removed each time.

[1] Merbaphen (novasurol) and a similar compound, salyrgan, are given in 0.5 to 2 c.c. doses intravenously at intervals of from two to five days.

On admission the patient was bed-ridden, and very dyspneic. There was massive dependent edema with marked ascites. The heart was enlarged, the pulse slow and irregular, and auricular fibrillation was present. The systolic blood pressure was 170 and the diastolic 110. There was moderate secondary anemia. The fundi revealed moderate arteriosclerosis of the hypertension type. The urine contained a small amount of albumin, a few red blood cells and white blood cells, and a few casts. The blood urea was 57 mg. for each 100 c.c. The carbon dioxid combining power of the blood plasma and the blood chlorids were normal. The test of hepatic function showed dye retention 4, and the serum bilirubin was 2.1 mg. for each 100 c.c. The diagnosis was uncompensated myocardial degeneration with auricular fibrillation, and portal cirrhosis.

The patient was placed on a low-salt, low-fluid diet[1] containing 1500 calories, and was given 5 to 9 gm. of ammonium chlorid daily and from 1 to 1.5 c.c. of merbaphen intravenously at intervals of a few days. He was

TABLE 1

CASE 1

Date.	Weight, kg.	Fluid intake besides that in food, c.c.	Ammonium chlorid, gm.	Merbaphen, c.c.	Blood pressure.		Urine volume, c.c.	Phenolsulphonephthalein output, per cent.	Hepatic function dye retention, grade.
					Systolic.	Diastolic.			
1/21/25	111.0	400	7.5		170	110	550		4
1/24/25	109.5	600	25.7	0.75			550		
1/25/25	108.6	400	34.9	1.0			2,850		
1/28/25	103.5	100	62.7	1.0	168	110	3,100		
1/30/25	97.7	200	81.1	1.0	160	110	4,600		
1/31/25	93.6	100	90.4		150	110	2,350		
2/ 7/25	86.1	200	114.4		140	90	1,150	40	
2/14/25	79.0	0	(1)		150	80	600		2
2/21/25	77.8	400	(2)		150	90	1,300		
3/ 2/25	75.0	400	159.4	1.0	180	100	3,100		2
3/ 7/25	71.3	200	177.0	1.5	130	90	2,000		
3/30/25	71.3	1,000	(3)		180	100	700	40	
6/25/26	70.0				170	100		50	0

(1) Discontinued from 2/1/25 to 2/5/25.
(2) Discontinued from 2/10/25 to 2/26/25.
(3) Discontinued from 3/11/25 to 3/21/25.

[1] The low-salt, low-fluid daily diet contains 800 c.c. of water and ions as follows: sodium 0.49 gm., potassium 1.76 gm., calcium 0.23 gm., magnesium 0.20 gm., chlorin 0.74 gm. Six hundred cubic centimeters of water besides that in the food is allowed.

in the hospital several weeks and lost 39 kg. in weight. At the time of his dismissal he looked and felt well. The tests of renal function were normal. The test of hepatic function showed dye retention 2, a decided improvement on that at the time of admission.

The patient returned June, 1926 for reëxamination. He appeared healthy. There had been no recurrence of the edema or ascites and the weight had remained between 70 and 72 kg., the same as when he was dismissed sixteen months previously. He had not found it necessary to use either ammonium chlorid or merbaphen, although he had adhered to the diet. He still had bradycardia, the pulse rate being 44 and irregular, and the heart showed auricular fibrillation with evidence of auriculoventricular block. The hemoglobin was 87 per cent, and the erythrocytes numbered 4,960,000. The tests of renal and hepatic function were negative (Table 1, page 606).

Case 2.—A man, aged sixty-one, registered at the Clinic March 1, 1926, complaining of swelling of the abdomen and legs of one year's duration. On three occasions the patient had had hospital treatment elsewhere with good results, except the last time, in November, 1925, when he was only moderately benefited. Dyspnea had been noted only when the edema was marked.

TABLE 2

CASE 2

Date.	Weight, kg.	Fluid intake besides that in food, c.c.	Ammonium nitrate, gm.	Merbaphen, c.c.	Blood pressure.		Urine volume, c.c.	Phenolsulphonephthalein output, per cent.	Hepatic function (dye retention), grade.
					Systolic.	Diastolic.			
3/ 1/26	108.2			0.5				25	
3/ 2/26	104.5	600	8		190	90	1,450		
3/ 5/26	103.4	600	46	2.0	180	70	10,600		
3/ 6/26	93.2	600	58		180	70	3,750		
3/ 9/26	89.5	600	94	2.0	180	100	3,900		
3/10/26	81.4	600	106		170	90	3,160		
3/11/26	79.6	200	118		150	86	2,600		
3/12/26	75.9	400	130		180	90	1,800		
3/13/26	75.5	400	142		160	80	1,675		
3/14/26	74.5	400	154		156	90	1,650		
3/21/26	70.9	500	200		140	80	900	40 (3/18/25)	2
4/21/26	70.9	500			140	80	550		2

There was marked dyspnea with Cheyne-Stokes' breathing, and massive edema involving the hands, abdominal wall, abdominal cavity, back, scrotum, thighs, and legs. The heart dulness measured 20 cm. and there was auricular

fibrillation. The systolic blood pressure was 200 and the diastolic 120. There was no anemia. The fundi showed mild arteriosclerosis of the hypertension type. The urine contained a trace of albumin, the phenolsulphonephthalein return was 25 per cent, the blood urea 50 mg., the carbon dioxid combining power 61 per cent by volume, and the blood chlorids 615 mg. The test of hepatic function carried out March 17, three weeks after admission, showed dye retention 2 with normal serum bilirubin. The diagnosis was myocardial degeneration with severe decompensation and auricular fibrillation, portal cirrhosis, benign hypertension, and general arteriosclerosis.

The patient was placed on a low-salt, low-fluid diet and given 12 gm. of ammonium nitrate daily, combined with merbaphen intravenously in doses of 2 c.c. at intervals. The first fourteen days in the hospital the patient lost 33.5 kg., and when dismissed had lost 37.5 kg. The heart dulness now measured 17 cm. and auricular fibrillation still persisted. The systolic blood pressure was 140 and the diastolic 90. The urine, the blood urea, carbon dioxid combining power, and blood chlorids were normal. There was no change in the hepatic dye retention test from that observed March 17. The change in the patient's appearance after three weeks' treatment was striking. He had been an extremely sick, dropsical individual and he now appeared and felt well (Table 2, page 607).

Case 3.—A man, aged fifty-one, entered the Clinic June 11, 1926, complaining of swelling of the legs which had begun a year previously. The swelling had been intermittent until March, 1926, when an attack of influ-

TABLE 3

CASE 3

Date.	Weight, kg.	Fluid intake besides that in food, c.c.	Ammonium nitrate,[1] gm.	Merbaphen, c.c.	Blood pressure.		Urine volume, c.c.	Phenolsulphonephthalein output, per cent.	Hepatic function (dye retention, grade.
					Systolic.	Diastolic.			
6/11/26	115.5	500	4	0.5	170	100	750	45	
6/14/26	103.0	300	34	2.0	166	120	7,350		4
6/18/26	102.0	400	74	2.0	170	95	5,550		
6/22/26	89.0	400	114	2.0	170	90	4,900		
6/29/26	73.1	500	184	2.0	155	70	3,050		2
7/ 7/26	64.8	450	254	(Discontinued)	120	60	900	50	
7/11/26	64.6	500			120	60	900		2

[1] Ammonium chlorid and ammonium nitrate are administered in amounts of 9 to 12 gm. daily in divided doses, given in capsules or enteric coated tablets.

enza was followed by a recurrence of the edema and the appearance of ascites which had gradually increased. The patient stated that for the last year he had been very short of breath and frequently had had to sleep in a sitting posture.

On examination the patient was pale and showed marked orthopnea and Cheyne-Stokes' breathing. There was massive edema of the arms, chest wall, abdominal cavity, scrotum, thighs, and legs. The heart was greatly enlarged, but regular in action. The systolic blood pressure was 170 and the diastolic 100. The hemoglobin (Dare) was 53 per cent and the erythrocytes numbered 3,780,000. The fundi showed mild signs of arteriosclerosis of the hypertension type. The urine contained some albumin. The phenolsulphonephthalein test of renal function gave a return of 45 per cent; the blood urea was 47 mg., the carbon dioxid combining power was 53 per cent by volume, and the blood chlorids were 635 mg. The test of hepatic function revealed dye retention 4 with normal serum bilirubin.

The patient was placed on the low-salt, low-fluid diet and given 10 gm. of ammonium nitrate daily combined with 2 c.c. of merbaphen intravenously at intervals. In the twenty-five days the patient was in the hospital he lost 50 kg. in weight. As in the first two cases, the change in appearance, and absence of symptoms in the space of three weeks was remarkable. On his dismissal the systolic blood pressure was 145 and the diastolic 70. The urine was normal, and the phenolsulphonephthalein return was 50 per cent; the blood urea was 53 mg., the carbon dioxid combining power 49 per cent, and the blood chlorids 575 mg. The test of hepatic function showed dye retention 2, which had on admission been 4 (Table 3, page 608).

DISCUSSION OF CASES

These three cases afforded a basis for the use of certain diuretics in the treatment of cardiac edema. Digitalis and caffein were not used. The marked diuresis was produced by the combined use of acid-producing salts and merbaphen. It is worthy of note that the first patient eighteen months ago responded remarkably well to the combined use of ammonium chlorid and merbaphen and lost 39 kg. during the course of treatment. This loss of weight was chiefly due to the elimination of edematous fluid. It should be emphasized that in this case there has been no recurrence of the symptoms. The splendid reaction of the other two patients to the diuretics occurred more quickly and the loss of weight was greater than in Case 1. Whether this will be permanent as in Case 1 still remains to be seen.

One of us (Jacobs) has demonstrated in himself and in approximately fifteen patients, including those in Cases 2 and 3, that ammonium nitrate is a suitable substitute for ammonium

chlorid. Ammonium nitrate is nontoxic, more easily taken, and is much less likely to cause nausea than ammonium chlorid. It seems, if anything, to cause more rapid and marked diuresis than ammonium chlorid. The chemical action of ammonium nitrate in the body is similar to that of ammonium chlorid, in that both cause an increased urinary output of acid, chlorin, ammonia, and total inorganic base. The exact mechanism of the action of these acid-forming salts is not entirely understood, but we do know that the ammonium radical forms urea quickly and the acid ion must play the predominating part in causing diuresis. In other words, the ammonium salts of inorganic acids afford an easy vehicle for the administration of these acid ions.

The diuretic action of organic mercury compounds has been shown not only to cause increased elimination of water, but also of sodium, chlorin, and often potassium, with little or no change in the acid-base regulation of the body. Thus, the combined action of an acid-producing salt and an organic mercury compound is additive; they both cause an increased excretion of water, sodium, and chlorin.

One of the most interesting aspects of the use of these diuretics in cases of cardiac edema is the undoubted improvement in the heart's action which follows their use. A factor in this improvement in cardiac action is the release of peripheral resistance due to the removal of excess fluid from the tissues. One would naturally expect that an increased transfer of fluid from the tissues to the blood would add to the embarrassment of an already weakened cardiac muscle, but apparently the release of peripheral resistance more than compensates for this increased load.

Following the removal of large amounts of fluid by diuresis, we must study each case further in regard to tolerance for water and salts, as we study the tolerance of the diabetic patient for sugar. Certain of these patients, by adhering to a low-salt, low-fluid diet, will have no recurrence of edema or ascites. Others may need to take moderate doses periodically of one of the acid-forming salts, while still others may require, in addition, injections of merbaphen once weekly or fortnightly to control the edema.

FOUR CASES OF ATYPICAL VASCULAR DISEASE AFFECTING THE EXTREMITIES

EDGAR V. ALLEN AND GEORGE E. BROWN

Many cases of localized vascular diseases of the extremities are clearly defined and present no serious problems in diagnosis. For this we owe a great deal to the original studies of Raynaud, Weir, Mitchell, and Buerger. There remains, however, a group of cases (with vascular disturbances of the extremities), the clinical features of which are not clear, are difficult to evaluate, and present real difficulties in diagnosis and treatment. The entire group of localized vascular diseases is not well understood nor clearly differentiated, as is demonstrated by the fact that less than 20 per cent of the cases of thrombo-angiitis obliterans that have been observed in the Clinic were correctly diagnosed.

A workable classification of these diseases is useful and simplifies their diagnosis. There are two main types of arterial vascular diseases which are classifiable on the basis of their functional or organic origin. Each of these has a local or general distribution (Table 1, p. 612). Organic or obliterative lesions of a localized nature are mainly of two types: thrombo-angiitis obliterans or Buerger's disease, and endarteritis obliterans or arteriosclerosis with or without superimposed thrombosis, including so-called diabetic gangrene. The clear-cut separation of the organic and the vasomotor types is usually decisive and determined by the presence of closed or open vessels of the part. There still remains a group of cases in which this differentiation is beset with difficulties and may be impossible. Vasomotor phenomena often exist in the presence of obstruction of the arteries, and gangrene is observed with open vessels proximal to the gangrenous area. To illustrate certain of the diagnostic problems arising in the study of these cases four cases are presented bringing out definite defects in

TABLE 1

TENTATIVE CLINICAL CLASSIFICATION OF ARTERIAL VASCULAR DISEASES

Functional or vasomotor types	Local distribution	Vasoconstricting types	1. Multiple-phase color reaction; Raynaud's disease
			2. One-phase color reaction; acrocyanosis, dead finger, local syncope
		Vasodilating types	Erythromelalgia
	General distribution	Vasoconstricting types	Primary or essential hypertension, early stages
		Vasodilating types	Primary or essential hypotension
Organic types	Local distribution		1. Arteriosclerosis, endarteritis obliterans, with or without thrombosis; diabetic gangrene
			2. Thrombo-angiitis obliterans
			3. Simple thrombosis or embolism
			4. Arteritis of known infectious origin (rheumatic, syphilitic)
			5. Aneurysm with or without thrombosis
	General distribution	Arteriosclerosis:	
			1. Primary
			2. Secondary to hypertension

the clinical picture which make the diagnoses difficult or impossible.

REPORT OF CASES

Case 1. Thrombo-angitis obliterans with extensive gangrene and complete absence of pain.—A man, aged forty, came to the Clinic September 24, 1925, with gangrene of the right foot and gangrenous ulcers over the right knee. During the years 1919–1920 calluses on the ball of the right foot and mild pain with exercise had appeared. Because of the pain in the calluses, they were incised in January, 1921, and the second, third and fifth toes were amputated for reasons unknown to the patient. The plantar incisions failed to heal and gangrene developed three days after operation. Healing was delayed for six months. In July, 1921 the great toe of the right foot was amputated elsewhere in the absence of pain or gangrene, and again six months were required for complete healing. In the interval between December, 1921 and August, 1925 there were no symptoms. In August, 1925 a small ulcer appeared spontaneously in the dorsum of the right foot which gradually became gangrenous and increased in size. Because of a slightly positive Kolmer reaction of the blood, a provocative test was made and the Wasser-

mann reaction was then three times strongly positive. Arsphenamin treatment was started when the ulcer was about 3 cm. in diameter and there was some tendency to heal. Exfoliative dermatitis developed and the gangrene spread rapidly. Gangrenous ulcers developed over the right knee and sacrum two weeks before admittance and progressed steadily. Never at any time had there been fatigue, claudication, or phlebitis. No color changes occurred other than those associated with gangrene.

Examination showed generalized exfoliative dermatitis; marked gangrene of the right foot with a gangrenous slough on the dorsum exposing the tendons, and but one toe remaining on the foot. There was a large ulcer over the right heel, several ulcers over the right knee and upper end of the tibia and a decubitus ulcer, over the sacrum. There was no pulsation in any vessels of the right extremity below the median femoral region. The left femoral, popliteal and posterior tibial arteries were pulsating, but there was no pulsation in the dorsalis pedis. With elevation of the right foot, there was pallor 3 and when dependent, rubor 2. The laboratory tests showed negative Wassermann reaction, normal urine, and blood chemistry. The blood sugar was 92 mg. for each 100 c.c. of blood. The erythrocyte count was normal, and the leukocytes numbered 13,600. The roentgenogram of the vessels of the leg did not reveal calcification. The diagnosis was obliterative vascular lesion involving both lower extremities, probably thromboangiitis obliterans, with gangrene of the right foot and arsenical dermatitis.

Two days after the patient's admittance amputation was performed above the right knee and uneventful healing followed in twenty days. The exfoliative dermatitis cleared rapidly. The gangrenous area over the sacrum sloughed and was healing when the patient was dismissed from observation.

Dissection of the femoral, popliteal, and proximal portion of the posttibial arteries and veins showed them to be so firmly bound together that separation was impossible. The anterior tibial nerve was also included in the periarterial binding for a portion of its course. In the popliteal region the inflammatory reaction was more marked and more acute than in the femoral or dorsalis pedis region. The lumen of the vessels was closed with what was apparently a white organized thrombus (Fig. 79). Microscopically marked periarterial fibrosis and a large number of newly formed blood vessels are shown (Fig. 80). The lumen was filled with an organized thrombus of a cellular nature in which canalization was incomplete. Few newly formed vascular channels were present in the walls of the vessels.

Comment.—This case presents many interesting points, among which complete absence of pain is most remarkable. Long association with patients with thrombo-angiitis obliterans impresses on one the severity and constancy of this symptom in the presence of trophic disturbances or gangrene. Usually the pregangrenous pain is mild, is confined to definite situations, is caused by exercise and relieved by rest; there is claudication with pain. With the development of ulcers or gangrene, this pain is

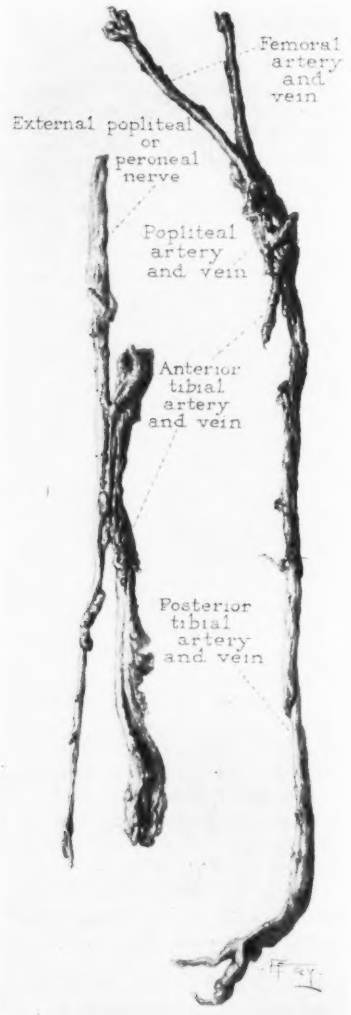
Femoral artery and vein
External popliteal or peroneal nerve
Popliteal artery and vein
Anterior tibial artery and vein
Posterior tibial artery and vein

Fig. 79.—Dissected vessel and nerve of amputated limb. Note the perivascular binding.

sharply accentuated, severe and continuous so that ordinary measures for relief are without avail. Severely afflicted patients sit upright in bed all night, rocking back and forth, rubbing the affected limb and smoking almost constantly. Frequently, they do not remove their clothes for weeks and sleep only in short naps from which they awaken unrested. They develop a distaste for food, lose weight, become wan, hollow eyed, and sunken cheeked.

Fig. 80.—Lumen of artery filled with organized thrombus. Canalization incomplete.

The continual pain is demoralizing and they beg for relief, frequently plead for amputation, and when operation is performed, look back without regret to the loss of the limb. This case is one of the few we have seen in which extensive gangrene was present without severe pain. An interesting feature is the involvement of the anterior tibial nerve in periarterial fibrosis in the absence of pain. The absence of pain could not be attributed to treatment for syphilis since there was no pain before

the institution of arsenical treatment. The absence of fatigue and claudication is very rare in association with a lesion sufficient to produce extensive gangrene. These symptoms are frequently absent in long-standing cases when there is no gangrene, and we interpret this as evidence of sufficient collateral circulation to keep apace with the progressive obstruction.

This patient was in the age group for thrombo-angiitis obliterans, as the ages of 78 per cent of our patients when first seen were between thirty and forty-five. He was of Scotch-Irish birth, a corroboration of the fact that this disease is not limited to the Hebrew race. Only 42 per cent of our series of over 150 patients were Hebrews. Absence of chronic superficial phlebitis is not uncommon, as this finding was present or had occurred in only 33 per cent of our cases.

The impaired renal function was unexplained, but could not be connected with the vascular condition. The possibility of arsphenamin damage to kidneys must not be overlooked. There is some reason to believe that treatment by arsenic in the presence of impaired circulation was responsible for the gangrene in the proximal areas. The abnormal calluses are interpreted as early trophic changes. The production of gangrene by slight trauma is characteristic of what occurs in the obliterative vascular lesions. Probably gangrene would have occurred despite injudicious surgery. The absence of pulsation in the vessels of the feet indicates more radical treatment. Thirty-six per cent of all of our cases of gangrene with thrombo-angiitis obliterans were initiated by incisions made by physicians.

This case presented a problem in diagnosis. In view of the positive history of syphilis one wonders what part it could play. Since the pathologic changes found in the amputated limb were characteristic of those in thrombo-angiitis obliterans, there is no evidence to show that syphilis was an etiologic factor. There is no proof that syphilis can produce an obstructive lesion of the larger vessels. Syringomyelia was excluded by the absence of neurologic data.

Case 2. Arterial gangrene with absence of pulsations in the vessels of the foot, but without obliteration.—A man, aged forty, came to the Clinic August 5, 1922, complaining of a nonhealing ulcer over the fourth and small toes of the left foot. In December, 1921, after having worn a new pair of shoes, a painful callus formed over the base of the small toe and fissures in the skin followed. Mercurial ointment was used, with improvement. Three months after the onset the patient lanced the area and considerable pus drained. The incision failed to heal in spite of rational treatment, and three months later a small painful, rapidly growing ulcer appeared. The pain was intense and continuous and was partially relieved by a dependent position and exercise. At no time had there been phlebitis, fatigue, or claudication. Color changes occurred only coincidental with gangrene.

Examination showed a few enlarged tender glands in the left inguinal region. There was mild edema of the right leg to the knee. The left leg

Fig. 81.—Gangrene and trophic changes in the left foot.

(Fig. 81) was red, cold and edematous, and there was a gangrenous area measuring 5 by 6 cm. on the dorsum of the foot involving the fourth and fifth toes. The fifth toe was gangrenous. The left foot showed rubor 3 when dependent and pallor 3 when elevated, indicating a deficiency in the supply of blood. No pulsation could be felt in the left popliteal, dorsalis pedis, and posterior tibial arteries. The right foot showed no change in color with postural change and the main arteries of the right foot and leg were pulsating normally.

The Wassermann test on the blood and spinal fluid was negative. Smears from the ulcer showed staphylococcus. The vessels of the legs were not visible by roentgen-ray. There was no roentgenographic evidence of spina bifida. Tests of the urine, blood chemistry, hemoglobin, and renal function test showed nothing abnormal. The blood count was normal. A provisional diagnosis of thrombo-angiitis obliterans with gangrene was made.

The patient was treated by various local measures and large amounts of Ringer's solution internally without improvement. The edema diminished markedly with rest. The ulcer did not grow larger, but a small perforated ulcer appeared at the base of the third toe. Mild edema and inguinal adenopathy persisted and the pain became so severe that amputation was performed below the knee forty-one days after admittance. Healing was complete in twenty days.

The surgeon reported that the condition was not typical of an obliterative vascular lesion; the walls of the vessel were not thickened and the lumens of the arteries were apparently free.

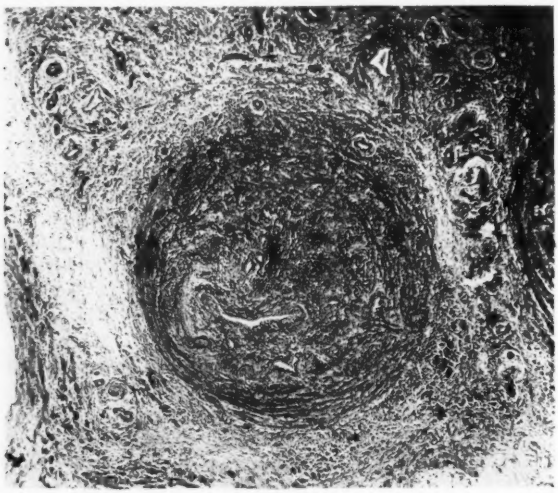

Fig. 82.—Periarterial fibrosis. Complete obliteration of lumen with organized thrombus.

The vessels of the leg were dissected into the finer palmar branches and no occlusion was found. All the arteries on section showed a patent lumen and normal walls. The pathologist's report on the ulcer was simple tissue hyperplasia. The lumens of the vessels were patent and there was no evidence of thrombus. The final diagnosis was indeterminate.

The subsequent course was uneventful for three years. The patient then stated in a letter that there seemed to be a similar condition in the right leg, and six months later he stated that he had injured this foot and a slowly healing ulcer had resulted. He returned to the Clinic May, 1926. An ulcer had occurred spontaneously on the right foot a year previously and had healed in three weeks. In November, 1925 he had dropped a plank on the right foot and a progressive, excessively painful gangrenous ulcer occurred

on the lateral aspect. Cold, elevation, and exercise accentuated the pain. For two months prior to his admittance to the Clinic he had been unable to lie in bed without hanging the foot over its edge. He had lost sleep and weight and had become gaunt and hollow eyed.

The examination showed the right ulnar and radial vessels to be pulseless and there were no pulsations in the arteries of the right leg below the upper femoral region. There was marked rubor of the foot in the dependent position and marked blanching when elevated. There was a gangrenous ulcer about 8 cm. in diameter on the outer border of the right foot, and another 2.5 cm. in diameter on the inner border of the foot. The diagnosis was thrombo-angiitis obliterans with vascular occlusion of the right hand and gangrene of the right foot, and amputation was performed as soon as possible because of the severity of the pain and extensiveness of the gangrene. Healing was uneventful.

Dissection of the vessels of the leg showed vascular occlusion and perivascular fibrosis and binding. Microscopically the small arteries showed almost complete obliteration by an organized thrombus with marked cellular infiltration. There was marked perivascular fibrosis and many newly formed blood vessels in the walls of the vessels and surrounding fibrous tissue (Fig. 82).

Comment.—A feature in this case is the absence of vascular obliteration in the presence of gangrene of the left foot, and symptoms indicating arterial block. The possibility of nonvascular gangrene was considered, but ruled out because of insufficient trauma, absence of neurologic change or malignant disease. There were no clinical data to indicate a vasomotor disturbance such as Raynaud's disease, as at no time were there pulsations in the vessels and there were no color changes initiated by thermic or psychic factors. The pain was constant and never paroxysmal and at no time was there complete restoration, as is observed in Raynaud's disease. The color changes with change in position indicated vascular occlusion. Examination of the vessels of the amputated limb threw no light on the etiology, and it was not until a similar condition developed in the opposite extremity which was amputated that the diagnosis of thrombo-angiitis obliterans could be made with certainty.

The pathologic study of the vessels of the right leg showed conclusively that the lesion characteristic of Buerger's disease was present. The absence of pulseless vessels and no demonstrable occlusion in the left leg indicated that the obliterative lesion was above the point of amputation and the empty vessels

below. Sufficient minor collateral branches were probably established to maintain a viable stump. The subsequent development of the process in the opposite foot and hand and subsequent amputation of the foot revealed the nature of the disease. Thrombo-angiitis obliterans is bilateral in most cases.

Case 3. Gangrene of the toes with pulsating arteries of the foot. Temporary relief from pain by radium chlorid.—A man, aged forty-six, came to the Clinic September 6, 1925, complaining of pain, redness, and gangrene of toes and feet. Three years previously he had had bilateral superficial phlebitis for a short time, following which he was fairly normal for two years except that his feet were cold and slightly blue. One year before admittance he was awakened by severe pain in the left third toe, and on inspection found it bluish black. This disappeared, and several times afterward the toe had been deeply cyanotic, but was not definitely gangrenous. This was accompanied by pain. Eight months later the second toe on the right foot had been similarly affected. This cleared up, but later recurred. The pain was very severe, with only slight relief from posture and other measures. There had never been claudication or symptoms of fatigue with exercise.

At the time of examination both feet were cold, red, and swollen. The third toe on the left foot and the second toe on the right foot were gangrenous; lymphangitis extended up the left leg in streaks and the glands in the left groin were tender and red. The arteries of both legs and feet were pulsating normally. Elevation of the feet produced blanching 2, and in the dependent position there was quick return of rubor 3 in the toes and distal half of the feet. The rate of heat elimination determined by the foot calorimeter was low. Microscopic examination of the nail-fold capillaries showed an occasional dilated loop, but most of them appeared normal, with some slowing of the rate of flow. The neurologic examination was negative. The blood and spinal fluid Wassermann tests were negative. The test of renal function showed 50 per cent return of the dye in two hours. The number of erythrocytes and the blood chemistry were within normal limits. There was slight leukocytosis during the course of the lymphangitis.

A diagnosis of diabetes, thrombo-angiitis obliterans, and nephritis had been made previously. A tentative diagnosis was now made of thrombo-angiitis obliterans with sudden or acute thrombosis in the distal vessels of the feet. The lymphangitis was considered as a sign of secondary infection.

The pain in the gangrenous area was very severe, but was completely relieved during the period of observation by 50 mg. of radium chlorid given intravenously. The lymphangitis, which extended to the left groin and was associated with marked febrile and leukocytic reaction, subsided under rational treatment. The following day there was another febrile reaction and erysipelas developed over the left knee. Recovery was uneventful in eleven days. The second toe of the left foot regained some normal color, but the

third toe on the right foot remained gangrenous and was amputated. There was practically no bleeding when the incision was made.

Microscopically, practically all the small vessels of the toe which was amputated showed thrombosis and organization with very little canalization (Fig. 83). There was marked vascularization in the surrounding tissue; a few purulent foci were present.

Healing occurred by primary intention. The patient was dismissed from observation on the fifty-fifth day after his admittance to the Clinic,

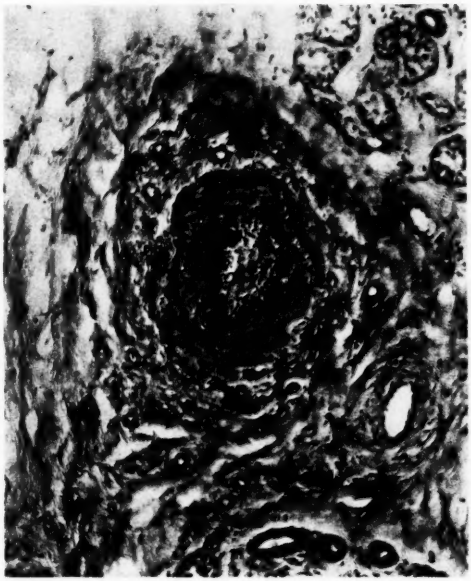

Fig. 83.—Complete occlusion of artery with organized thrombus. Note the many newly formed blood vessels.

entirely free from pain and much improved in general health. One month later a letter stated that the third toe of the left foot was again semigangrenous, and six months later a large ulcer had appeared on the left great toe. The patient thought amputation would be necessary.

Comment.—Gangrene of the toes in the presence of pulsating pedal arteries is unusual, and is suggestive of an obliterative lesion limited to the distal vessels of the feet and the toes. Absence of fatigue and claudication in the arches or calves partially supports

this. The history of a preceding superficial phlebitis makes the diagnosis of thrombo-angiitis obliterans tenable. The fairly sudden onset of pain and discoloration in the toes indicated acute thrombosis and with the establishment of collateral circulation, with partial recovery. Embolus could not be excluded, but the recurrence in the same situation and in the opposite foot was against this premise. Relieving pain by the injection of radium chlorid is not uncommon. Of twelve patients thus treated, five were completely relieved for periods up to eight days. Amputation of the toe was justified in the presence of open vessels proximally.

Case 4. Thrombo-angiitis obliterans showing remission of symptoms in warm weather. Involvement of four extremities. History of phlebitis of veins of arms.—A man, aged forty-nine, came to the Clinic January 2, 1925, complaining of sore feet and discoloration of the tip of the second toe on the right foot. Ten years before he had had claudication of the calves with exercise. This lasted for one month and disappeared for five years. One year later, following chilling of the feet, he noticed soreness in the soles and pain in the calves which was worse at night and was independent of exercise. The next year the soles of the feet became suddenly sore and were very cold, but no change in color was noticed. The following summer his feet had been entirely symptomless, but in the fall he began to have persistent soreness in the feet and calves. This continued through the winter with no definite change, and in the spring all symptoms disappeared. Again in the late summer persistent aching began in the calves, and in the winter became so severe as to interfere with sleep and ordinary daily routine. The pain was progressive. Four months before his admittance to the Clinic most of the pain had localized in the right leg and foot, and was sharp, stinging, and throbbing. For six weeks the patient had been unable to sleep without hanging the right leg out of bed. For the last two years there had been numbness, swelling, aching and claudication, and pain in both hands. During the same period he had recurrent superficial phlebitis over the legs, thighs, and arms. Three weeks before admittance a cow had stepped on the right foot and injured the second toe slightly. Following this there was severe pain. A blood blister appeared which was opened by the patient and the tip of the toe became gangrenous. An ulcer followed and persisted. In the last year he had lost 20 pounds in weight.

Examination showed moderate emaciation. The tonsils were enlarged and septic. There was marked pyorrhea. Both feet were cold, cyanotic, and perspiring. The skin and nails of the toes of the left foot were thickened and roughened. The second toe of the right foot was gangrenous and there was edema 3 of the ankle. The skin was tense, shiny, and reddened. The main arteries of the left arm and the right foot and leg were pulsating normally.

The dorsalis pedis and posterior tibial arteries of the left foot were pulseless. The left foot when elevated showed pallor 3, and rubor 2 when dependent. The right foot when elevated showed pallor 3, and rubor 2 with a bluish cyanosis when dependent. The right radial artery showed diminished pulsation.

The blood Wassermann test was negative, the erythrocyte count, blood chemistry, and renal function were normal. Examination of the urine was negative. The roentgenogram showed periapical infection in two teeth. The arteries of the legs were not visible by the roentgen ray. The systolic blood pressure was 130, the diastolic 80. A diagnosis was made of thromboangiitis obliterans of both feet with gangrene of the second toe of the right foot.

Sodium citrate was given intravenously and alcohol dressings and heat applied locally. Gangrene and pain progressed in the second toe of the right foot and it was amputated at the proximal joint. Healing was satisfactory. Seventy-two days after his admittance to the Clinic the patient was dismissed from observation free from pain and with a well-healed amputation stump. One year later he was free from symptoms except for slight aching in the feet in cold weather.

Microscopically the main artery of the toe was patent and did not show thrombosis. The smaller arteries and veins were occluded by partially organized thrombi. There was marked vascularization of periarterial fibrous tissue, but no evidence of acute infection.

Comment.—The remissions in claudication are not usual. Most cases progress gradually from onset to gangrene and amputation or to compensation. The interpretation of the irregularity of the fatigue or claudication is difficult. Probably the underlying process is vascular obliteration with anoxemia and claudication. Then follows the establishment of collateral circulation sufficient to give symptomatic relief, then further progression of the obliterative lesion and subsequent return of symptoms. This could be repeated several times. The disappearance and reappearance of rest pain is significant, probably indicating subsidence and recurrence of the inflammatory process. The aggravation of pain in cold weather is usual. In 86 per cent of our cases the onset of pain appeared during the winter, and practically all of the patients were worse in cold weather. Superficial phlebitis in the veins of the arm is rare, while it is common in the legs. Involvement of all four extremities in Buerger's disease occurred in about 5 per cent of our cases. Careful examination of the ulnar and radial arteries will frequently show

obliteration of one of these vessels without symptoms. Thromboangiitis obliterans affects arteries as well as veins, the process of thrombosis, organization, and canalization, can be followed in the resected superficial veins, and probably indicates a similar course of events occurring simultaneously in the arteries.

THREE CASES OF IDIOPATHIC HYPERTENSION WITH A CONSIDERATION OF DIAGNOSIS, PROGNOSIS, AND TREATMENT

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We are presenting three cases of essential hypertension, which vary in severity, prognosis, and treatment. Since they typify the three forms of essential hypertension which we recognize, a summary of our working classification is given.

Essential or idiopathic hypertension (hypertension occurring independent of renal or other demonstrable disease) is variously known as vascular hypertension, hyperpiesia without renal involvement, and cardiovascular hypertension. It may be divided into two types, the benign and the malignant. Benign hypertension may be further subdivided into two rather ill-defined groups, the mild and severe. The differences between the benign and the malignant forms are striking and uniform. It is difficult on occasions, however, to make a sharp distinction between the mild and the severe forms of benign hypertension.

MILD BENIGN ESSENTIAL HYPERTENSION

This type of hypertension does not present a uniform picture, since the diagnosis is based more on a general clinical impression than on a hard-and-fast outline. Mild benign hypertension merges insensibly into the more severe form of the benign type, and there are many cases which possess some features of both. Whether or not a mild form of hypertension can progress to the severe form and eventually into the malignant is not known and can only be determined by prolonged observation. Certain it is that some patients tolerate relatively mild hypertension for years without serious complication and eventually outlive their normal ex-

pectancy, the hypertension having proved of no particular moment so far as life is concerned. More commonly, however, definite increase in the severity of the disease is noted with accruing years. Actuarial records indicate that the higher the blood pressure at any given age, the shorter is the life expectancy. In other words, a pressure of 180 systolic with a diastolic of 120 is of less serious import at sixty than at thirty. It is for this reason then that we attempt to classify our cases of benign hypertension as mild or severe.

It is obviously impossible to lay down a fixed rule for the diagnosis of mild essential hypertension, since the age factor is variable, and the duration and severity of symptoms, the degree of vascular and renal damage, and the response to treatment must all be taken into consideration. We feel, for example, that the following findings would suggest a case of mild benign hypertension: systolic blood pressure from 150 to 200 and diastolic from 90 to 110; few or mild subjective symptoms; little or no evidence of cardiac enlargement and renal damage; minimal fundal changes such as arterial constriction and arteriovenous compression, and prompt response to treatment.

SEVERE BENIGN ESSENTIAL HYPERTENSION

The difficulty and undesirability of establishing fixed values or boundaries applies equally to the severe type. It would be unreasonable to fix a systolic pressure of 200 mm. as the dividing point between mild and severe hypertension, without considering the other variable factors. The differentiation rests on a careful balancing of the significant elements in the age, history, physical findings, laboratory data, and the response to treatment. Given a patient forty years of age with systolic blood pressure between 200 and 250 and diastolic between 100 and 160, with subjective symptoms such as severe dyspnea, headache, and vertigo, with cardiac enlargement and some renal damage, with changes in the eye-grounds such as irregularity in the caliber of the arteries and with hemorrhages and exudates, consideration of the case in the category of severe benign hypertension would be amply justified.

MALIGNANT HYPERTENSION

Malignant hypertension, at the time when medical advice is sought, generally shows these characteristics: the victim is comparatively young (average age thirty-nine); there is surprising paucity of symptoms referable to the cardiovascular system (severe headaches and visual disturbances associated with nervousness and loss of weight and strength are the most common complaints); illness has been relatively brief (from three months to three years); systolic and diastolic pressures are high (systolic from 200 to 300, diastolic from 120 to 200) and in most cases respond poorly if at all to treatment; there is some degree of cardiac enlargement and peripheral sclerosis; neuroretinitis is out of all proportion to the degree of renal damage; renal function is fairly normal or but slightly diminished; the blood is chemically normal; no anemia is demonstrable; and what is most important, death from cerebral accident, or cardiac or renal decompensation, ensues within six months to three years.

For purposes of illustration three cases of hypertension will be discussed here: one of a fairly mild type of benign hypertension; the second, a more severe type of benign hypertension; and the third, malignant hypertension.

REPORT OF CASES

Case 1.—A married woman, aged fifty-four, came to the Clinic after about two years of failing health. She had first noticed palpitation and undue shortness of breath after exertion. Her physician found the blood pressure higher than normal; he prescribed meat-free diet and advised her to have all teeth extracted. Shortly afterward all but two lower incisors were extracted and she was told that the blood pressure had fallen. About three months before her admission to the Clinic the blood pressure rose to its former high level and she was placed on a very restricted diet and enjoined to touch no meat, eggs, butter, or salt. Subjectively comfortable at this time, save for undue dyspnea on exertion, she lost weight rapidly (15 pounds in three months) and strength under the dietary restrictions imposed. She was nervous and apprehensive. Sleep was much disturbed because of emotional instability, and weakness prevented her from performing her ordinary household duties. There were no other subjective symptoms.

On examination she weighed 104 pounds and was 5 feet 6 inches tall. The pulse and temperature were normal. The skin and musculature were flabby and toneless. Nervousness and apprehension were marked. The eye-grounds showed slight, uniform, constriction of arteries, but no edema,

hemorrhage, or exudate. The teeth were absent except for two normal incisors; the tonsils had been enucleated. The left border of the heart was 10 cm. from the midsternal line. The second aortic sound was accentuated and occasional extrasystoles were heard. The systolic blood pressure on admission was 190 and the diastolic 105. The brachial and radial vessels showed sclerosis 1. Repeated specimens of urine showed nothing abnormal but an occasional trace of albumin. The phenolsulphonephthalein return was 75 per cent in two hours. The water test showed a normal two-hour output of urine (1,200 c.c.) and specific gravity as low as 1.002. The concentration test yielded several specimens of urine with specific gravity of 1.020. Erythrocytes numbered 4,800,000, leukocytes 8,700, and the hemoglobin was 80 per cent. The blood urea was 11 mg. and blood creatinin 1.2 mg. for each 100 c.c. The blood chlorids were 615 mg. for each 100 c.c. The blood Wassermann test was negative. Roentgenograms of the chest were negative. The electrocardiogram showed nothing of significance. During the routine three-day period of rest in bed without medication the systolic blood pressure on successive readings dropped from 190 to 175, to 168, and finally to 150. The coincident diastolic readings were 105, 105, 100, and 80. She was then given 3 grains of sodium nitrite in ½-grain doses at one-half hour intervals. The systolic and diastolic blood-pressure readings were 200 and 120 at the start, and 150 and 90 at the end. She was placed in a tub of water at 105° F. for fifteen minutes. The systolic and diastolic blood pressures were 170 and 90 at the start, and 193 and 98 at the end.

This patient was given a balanced diet of 3,000 calories. She was repeatedly reassured as to the excellent condition of the cardiorenal system. She was told that the hypertension was as much an intrinsic feature of her bodily mechanism as her graying hair, and was advised not to spend time and money in a futile search for a will-o'-the-wisp cure. She was told that regularity of habits and freedom from mental and physical stress were of more value than the eradication of foci of infection, medicines, and diet. She was directed to rest nine hours at night and one hour at midday. Three grains of sodium nitrite were to be taken alternate days and she was to be examined periodically by her local physician. She was asked to return to the Clinic in from six to twelve months. At the time of her dismissal she had regained some weight, she was sleeping soundly, her nervousness and apprehension had lessened, and she was feeling better than she had in the previous three months. She was told that when she had recovered her normal weight her diet would be reduced somewhat.

Comment.—This is an example of fairly mild hypertension in an elderly patient. There were few signs of cardiorenal damage, and there were no subjective complaints other than apprehension and undue shortness of breath on exertion. This patient had been subjected to extensive extraction of teeth with the understanding that it might alleviate the high blood pressure; and when the pressure rose she had been restricted to an inadequate

diet. When seen at the Clinic she was obviously suffering from chronic starvation and its results, physical and nervous exhaustion. We felt that the first requisite was to reëstablish her nutritional balance and to restore, if possible, her weight and nervous control. To these ends we prescribed a well-balanced diet, and attempted to reassure her and to give her a general understanding of her disease.

Case 2.—A woman, aged thirty-four, came to the Clinic in 1923 complaining of constant fatigue, lack of strength, frequent severe occipital headaches, moderate undue dyspnea and palpitation on exertion, occasional swelling of the ankles, occasional black spots before the eyes associated with dizziness, and an unpleasant feeling of constriction or dull pain in the front of the chest. The first and only pregnancy, eight years before, had been complicated by typical eclamptic toxemia, and delivery occurred in the eighth month. The blindness, edema, albuminuria, and elevated blood pressure which had been present during the eclampsia disappeared rapidly after delivery, and six months later she was considered absolutely well. Four years later she nursed her husband through a long and distressing illness and finally collapsed under the strain. Her systolic blood pressure was found to be 190 at this time. She gradually regained her strength, but, the blood pressure remaining high, a meat-free diet was prescribed and her activity restricted. Two years before admission to the Clinic moderate nocturia had been manifested, but this had gradually disappeared.

The patient was well nourished, intelligent, and coöperative. She was 5 feet 6 inches tall and weighed 130 pounds. The pulse and temperature were normal. The eye-grounds showed slight constriction of arteries, but no edema, exudates, or evidence of hemorrhage were seen. The teeth were excellent; the tonsils were moderately infected. The apex beat was in the fifth intercostal space, 10.5 cm. to the left of the midsternal line. The first aortic sound was roughened and a definite diastolic murmur was heard to the left of the sternum at the base. The peripheral vessels were moderately sclerosed.

Repeated specimens of urine contained casts, pus, and varying amounts of albumin. During the water test 1,000 c.c. were passed in two hours and a specific gravity as low as 1.002 was obtained. The urine in a concentration test showed specific gravity of 1.017. On two examinations a return of 35 and 45 per cent of phenolsulphonephthalein was obtained. The erythrocytes numbered 4,350,000 and leukocytes 7,000; the hemoglobin was 85 per cent. Blood urea was 30 mg., creatinin 1.8 mg., and uric acid 4.2 mg. for each 100 c.c. The blood Wassermann test was negative. An electrocardiographic tracing afforded no significant findings.

During three days' rest in bed the systolic blood pressure varied between 160 and 200, and the diastolic between 120 and 130. The systolic pressure remained at 160 and the diastolic at 120 after 3 grains of sodium nitrite had been given. Corpus luteum similarly failed to influence the blood pressure,

but repeated hot baths (semi-emersion in water at 105° for fifteen minutes) showed a constant, though slight, tendency to depress the tension. Changes in posture (sitting, lying, and standing) had no effect on blood pressure, the readings being 180 for the systolic and 130 for the diastolic in all positions.

The patient was sent home with a strict regimen: nine hours' rest at night, one hour of midday rest, diminution of physical and mental stress to a rational minimum, "hypertension" baths three times a week, 3 grains of sodium nitrite daily three days a week alternating with the baths, and a diet of 2,500 calories containing 40 gm. of protein. She reported fully on her progress at intervals. The nitrites were discontinued after a few weeks because of unpleasant subjective symptoms. She adhered faithfully to the other injunctions, however, and led a quiet, orderly existence for three years.

In July, 1926 she returned to the Clinic for examination. She had had few headaches and but little vertigo since her first visit to the Clinic. Moderate palpitation and dyspnea had continued to appear after exertion. Exertion also brought on a rather sharp precordial pain just to the left of the sternum. There was no radiation of the pain, no sense of impending death, and no great associated distress. Nocturia, once each night, had appeared during the last year. In May, 1925 the tonsils were removed and for a few weeks thereafter the blood pressure was lower than usual. It soon sought its former level, however, and the average for the three years was 215 for the systolic and 100 for the diastolic. Black spots before the eyes were rarely evident and no edema of the ankles had been noted.

There were no abnormal physical findings other than those noted during the first examination. Two specimens of urine were quite normal aside from an occasional red or white blood cell. On the water test 1,100 c.c. of urine was eliminated and the urine diluted to a specific gravity of 1.001. On the concentration test specific gravity of 1.018 was obtained. The phenolsulphonephthalein excretion was 50 per cent. Erythrocytes numbered 4,090,000, and the leukocytes 8,000; the hemoglobin was 74 per cent (Dare). Blood creatinin was 1.2 and urea 22 mg. for each 100 c.c. of blood. The blood Wassermann test was negative. Roentgenograms taken of the heart at 6 feet were negative. The electrocardiogram showed no changes of importance.

The systolic pressure dropped from 208 to 142 and the diastolic from 140 to 98 after 3 grains of sodium nitrite had been given. The hypertension bath showed the same slight but definite tendency to lower the pressure as it had three years before. Changes in posture had no influence on the blood pressure.

Comment.—This is an example of a more severe type of benign hypertension with distressing subjective symptoms. Because of the history of eclampsia eight years before the patient's first admission the possibility of chronic glomerulonephritis was strongly considered. It was ruled out (or relegated to a minor position) because of the paucity of demonstrable renal damage,

the chemically normal blood, the absence of anemia, and the predominance of symptoms and signs of hypertension.

When the patient was first seen, three years before, the outlook appeared dubious. The occurrence of high diastolic pressures (from 110 to 130) in so young a patient suggested a rather serious prognosis as to life expectancy. It was with much interest, then, that she was studied on her second admission.

On a fairly strict regulation of life the patient had been quite comfortable, subjectively at least, definitely more so than previous to her first visit. The swelling of the ankles had disappeared; the headaches and vertigo were less frequent and less severe; her strength had increased and she was maintaining her normal weight. Except for nocturia and some degree of precordial pain after exertion she was in fairly satisfactory health. On physical examination no distinct increase in the extent of the disease was noted. The eye-grounds were unchanged and the cardiac dulness was no wider than on first examination. There was some improvement in the excretion of phenolsulphonephthalein and fewer pathologic constituents in the urine. The dilution and concentration factors were unchanged. Blood pressure readings showed a higher diastolic pressure than on the first visit, in spite of which the reaction to sodium nitrite was satisfactory on her second examination.

Case 3.—The patient, aged fifteen, was brought to the Clinic because of life-long enuresis. During the course of examination hypertension was found and attention was shifted to this feature. About four years before admission she began to have frontal headaches, generally over the right eye. Sleep always relieved the ache. Two years before admission glasses were fitted and some relief obtained. During the course of an acute illness about that time albumin was found in the urine, and a meat-free diet was prescribed. One year before admission the headaches changed in character and situation from frontal to occipital. During the previous six months occipital headaches had occurred almost daily, coming on in the early morning and persisting until sleep was obtained. Despite these headaches, she had attended high school and participitated in all the activities; indeed, she was considered the best female athlete enrolled. Two months before her visit to the Clinic, while running the hurdles, she slipped and fell to the floor. Immediately thereafter a typical left-sided Bell's palsy appeared. The paralysis gradually disappeared. She denied any history of undue dyspnea, palpitation, edema of ankles, dizziness, or visual disturbance.

The patient was tall, slender, and quite nervous. The eye-grounds showed edema of the disks and retinæ, marked constriction and tortuosity of arteries, and numerous patches of "cotton-wool" exudate. The carotid vessels appeared dilated and tortuous and showed systolic pulsations. The heart was not perceptibly enlarged and the sounds were normal save for a booming second aortic. The systolic blood pressure was 220 and the diastolic 145. Moderate peripheral sclerosis was present and there were slight traces of recent left-sided Bell's palsy.

Repeated specimens of urine were normal but for traces of albumin. The response to the water test and concentration test was quite normal, and 70 per cent of phenolsulphonephthalein was excreted within two hours. Erythrocytes numbered 4,630,000 and leukocytes 9,000; the hemoglobin was 80 per cent (Dare). There were 27 mg. of urea and 1.5 mg. of creatinin for each 100 c.c. of blood. The blood chlorids and carbon dioxid combining-power of the plasma were normal and the blood Wassermann test was negative. The electrocardiogram was negative. Roentgenograms of the chest, kidneys, ureters, and bladder were negative. The roentgen-ray failed to demonstrate calcification in the vessels of the extremities.

During three days of rest the systolic blood pressure remained at 200 and the diastolic at 135; after 3 grains of sodium nitrite had been given the systolic pressure was 190 to 200 and the diastolic 120 to 116. Neither luminal nor hot baths lowered the pressure. Toronto liver extract was similarly ineffective.

This patient was sent home on greatly restricted activity. Her parents were advised of the most unfavorable prognosis and asked to communicate with us at intervals.

Comment.—This is a typical case of malignant hypertension. The outstanding complaint was occipital headache. Absolutely no symptoms directly referable to the heart were found after careful questioning. The diagnosis rested on the changes in the eye-grounds which were striking and clear cut.

SUMMARY

Three cases representing the three varieties of hypertension are presented. The response to various methods of reducing blood pressure has been described together with other findings which make it possible to classify each case of hypertension. A study of these cases indicates that the levels of the systolic and diastolic pressures alone are not sufficient to determine the classification. Examination of the eye-grounds, appraisal of the cardiovascular system as a whole, and careful estimation of the renal

and cardiac functions must be carried out before a case can be classified. Without classification suitable treatment is difficult, and accurate prognosis is out of the question.

All of the patients had foci of infection. It has been our experience that the eradication of foci of infection in cases of hypertension has no beneficial effect on the hypertension itself; indeed, this practice may prove distinctly harmful if the hypertension is malignant. In the benign forms of hypertension we often suggest the eradication of foci more as a prophylactic than a curative measure.

The physician must know how the blood pressure will respond to certain measures, before he can advise his patients intelligently how to adjust their lives to the vascular handicap. This is determined by observation in hospital. First of all, the effect of absolute rest in bed is ascertained by putting the patient to bed and keeping him there for three days. Blood pressure is measured at frequent intervals during this rest period and the basal level of blood pressure is determined. Following this sodium nitrite is given ($\frac{1}{2}$ grain hourly for six doses) and the blood pressure is measured each hour during the day. The following day $\frac{1}{2}$ grain of luminal is given hourly for six doses, blood pressure being measured similarly. The following day the effect of fifteen minutes in a bath at a temperature varying from 100° to 105° F. is determined by taking the blood pressure before, during, and one, two, and three hours after the bath. Each of these last three tests is carried out on a different day, so that no delayed reaction from one agent will vitiate the results of another. In selected cases a foreign protein (typhoid vaccine) is injected with the idea of producing vasodilatation and systemic fever.

It will be seen that a patient can be accurately advised about the plan of life he must adopt when the results of these tests are available. In many cases we have found that prolonged rest alone is sufficient to lower elevated blood pressure. In this event patients are advised, for example, to spend nine to ten hours in bed each night and to lie down for one hour after lunch. They may also be asked to spend one day each week or one week out of every three months in bed. These frequent rest periods

together with some diminution of their former activities have proved of immeasurable benefit in many instances.

If nitrites or luminal prove to be of value, these agents are prescribed. If the warm bath is effective, this measure is advised daily or every second day, alternating with the administration of sodium nitrate. These measures, together with vacation periods free from attempts to break records in speed, strength, and endurance, go to make up part of the general plan of life for the patient with hypertension. Most patients soon find as a result of such careful living that hypertension is a condition with which one may live and live well with remarkably little discomfort.

Every patient is interested not only in how he is to live, but also how long. In a general sense, patients with uncomplicated hypertension who respond well to the tests described have an infinitely better outlook than those whose pressure is not lowered by any of these measures. The degree of response in many instances is directly proportional to the brightness of the outlook.

With reference to diet in uncomplicated cases we recommend moderate restriction in the total calories consumed and limitation of proteins to 60 gm. in twenty-four hours.

EFFECT OF INTRAVENOUS TREATMENT IN UREMIA

EDWIN G. BANNICK

Uremia is a term used to designate the clinical syndrome which accompanies the toxemia of renal insufficiency irrespective of its cause. Only the types that are associated with marked retention of the products of nitrogenous metabolism will be discussed here. True uremia in its chronic form is the typical and not infrequent termination of the third stage of chronic glomerular nephritis and chronic diffuse nephritis, and the late stage of chronic pyelonephritis and of renal sclerosis. Acute forms of uremia occur in certain acute and subacute types of nephritis and in acute exacerbations of chronic nephritis in any of the forms mentioned.

The treatment of any of these types of uremia is largely symptomatic and requires patience and perseverance. This is particularly true of the chronic forms in which sooner or later a fatal result is inevitable. Many physicians, realizing this, have despaired of intensive treatment, and have contented themselves by using the supportive measures with occasional purging and sweating.

In my observation of many patients with renal diseases at the Mayo Clinic opportunities have been afforded for the careful study of a considerable number of cases of true uremia, most of them of a chronic asthenic form, and the conclusion has been reached that by proper treatment and judicious hygienic measures, in certain cases of even the severe chronic form, patients may be made comparatively comfortable and life prolonged.

In a definite clinical group of cases it would seem that the proper treatment often calls for forced fluids, blood transfusion, and the intravenous injection of hypertonic solutions (usually

glucose) besides the usual supportive measures. The chief characteristics of this group can be briefly outlined:

The patients have asthenic uremia, severe acidosis, and moderate or severe anemia. They are nauseated, often vomit, and are extremely toxic. There is little or no edema, but often severe dehydration. There is marked retention of the waste products of nitrogenous metabolism, as represented by the urea and creatinin in the blood, and the kidneys are unable to concentrate urine. It would seem that the therapeutic indications in such a group are to attempt to overcome the dehydration, toxemia, and acidosis, to stop the vomiting and correct the anemia, to lower the level of the end-products of nitrogenous metabolism in the blood, to produce diuresis, and maintain compensatory polyuria.

GENERAL PLAN OF TREATMENT

When such a patient is assigned to the hospital an attempt is made to keep up a daily intake of from 2,500 to 3,000 c.c. of fluid and to give considerable carbohydrate. The fluid is given orally, rectally, and intravenously. It is given orally in the form of water, soda and water, or fruit juice; rectally in solutions of 5 per cent glucose or 5 per cent glucose and 1 per cent sodium bicarbonate, and intravenously in hypertonic glucose solutions, usually of a 10 per cent strength.

The intravenous administration of glucose is continued indefinitely, at least until the nausea and vomiting is controlled, and the patient is able to take sufficient fluid by mouth. Usually 1,000 c.c. of a 10 per cent solution is administered daily. As soon as the patient can retain solid food without discomfort he is given a diet containing 40 gm. of protein with a minimum of 1,500 calories and with some fruit juice between meals. After the severe toxemia is somewhat ameliorated the patient with severe anemia is given one or more blood transfusions. Usually 500 c.c. of citrated blood is given at a time and repeated in four or five days if conditions warrant it. In some cases in which the toxemia is controlled with extreme difficulty venesection is combined with transfusion; about 150 c.c. of blood is withdrawn and 600 c.c. of citrated blood injected. Besides these measures the

bowels are made to move daily, but the patients are rarely purged. Occasionally one of the more vigorous patients is sweated. Purging and sweating is reserved mostly for the uremic patients with edema, when fluids cannot be forced. All patients are supported according to orthodox principles and stimulated if necessary.

Intravenous treatment.—It is now generally conceded that sugar is the best kind of food for patients with various types of toxemia, especially those associated with severe acidosis; in these carbohydrates seem to have a definite protective value. When carbohydrates are burned they not only aid in the complete oxidation of fats with the lessening of acidosis, but they also spare the proteins, so that there is less nitrogen to be excreted by the kidneys. Water is very essential for this group of uremic patients. They are not edematous, but are more often dehydrated. They cannot concentrate urine, so the only way in which they can lower the urea and creatinin in the blood to any marked degree is by passing large amounts of this dilute urine. Water overcomes the dehydration and makes diuresis possible with the associated elimination of the nitrogenous end products.

The intravenous method of administering fluid and sugar in certain of these cases is employed for several reasons: An attempt to force fluids by mouth increases the nausea and vomiting; continued proctoclysis in large amounts interferes with the retention of the solution, and the subcutaneous method is often painful and does not afford sufficient concentration to be of much nutritive value. Hypertonic solutions of glucose, on the other hand, when given intravenously are almost painless; they diminish the nausea and vomiting, supply both fluid and food, and have additional properties of combating toxemia and acidosis. Titus,[6] Harding and Potter,[2] and others have shown without much doubt that this treatment has a definite value in the hyperemesis of pregnancy and in cases of nondiabetic acidosis. McVicar[3] has used it with 1 per cent solutions of sodium chlorid in treating the toxemia of high intestinal obstruction. The same reasoning would indicate its use in cases of uremia and acidosis.

The question arises of whether intravenous injection of 10 per cent glucose solutions has any diuretic value in these cases of

uremia and acidosis. Woodyatt, Sansum, and Wilder showed that the average normal adult at rest in bed began to excrete glucose in the urine with associated diuresis when the injection rate into the vein was more than 0.85 gm. for each kilogram of body weight an hour. Thus, by giving more than 63 gm. of glucose intravenously in an hour to a normal person weighing 70 kg. and resting quietly excretion of glucose with diuresis occurred. However, the authors emphasized the point that these data represented results on normal persons and that there were great variations in the limits of intravenous tolerance in different diseases.

In giving 100 gm. of glucose intravenously in 1,000 c.c. of fluid in forty-five or fifty minutes, as has been our custom in these cases, there should be some diuresis if subjects are normal, but in these cases of uremia with decreased permeability of the kidneys, it is doubtful how much diuretic property exists. Suffice it to say, that with the injection of 1,000 c.c. of 10 per cent glucose in forty-five or fifty minutes there is at least a tendency toward diuresis.

German writers[4, 5] recently have advised the intravenous administration of 20 to 30 per cent solutions of glucose in trying to control the toxemia of uremia. But they have given much less than 1,000 c.c. of fluid in these more concentrated solutions. Twenty per cent solutions have been used in some cases of my series in amounts varying from 500 to 1,000 c.c., but at present the 10 per cent strength is usually preferred, since more fluid can be given safely with this percentage strength. This is important in the group of nonedematous cases under discussion. In the more acute or subacute forms and in those in which there is some edema, and diuresis is the chief aim, 20 per cent or even stronger solutions are often advisable if given in smaller quantities or injected at a slower rate.

In considering the rationale of blood transfusions in these cases of uremia and severe anemia, the indications have been regarded as for any severe secondary anemia. French writers,[1] have gone a step further than this in stating that the improvement in anemia exerted secondarily a favorable action on the

azotemia. I have found that blood transfusions often improve the anemia and general strength of these patients and sometimes lessen the tendency to epistaxis which is often a troublesome complication. Very few untoward reactions from intravenous treatments have been noted. Following the blood transfusions in a few instances the patients had a slight chill followed by a little fever, but these reactions were not serious. Only one untoward reaction followed the intravenous administration of glucose. In this instance the patient developed pulmonary edema about ten minutes after 1,000 c.c. of a 20 per cent glucose solution had been given intravenously in fifty minutes' time. Venesection of 350 c.c. afforded prompt relief. This patient had severe myocardial degeneration, and undoubtedly the concentrated solution was given too rapidly.

This brings up a point emphasized by German writers.[4, 5] They advised extreme caution in the intravenous injection of hypertonic solutions if patients had a badly diseased myocardium. This is certainly a factor to be reckoned with, but in none of the cases in this series did the cardiac condition preclude intravenous treatment, and the only bad reaction was the one cited. Some of the patients had severe myocardial disease, as was usually confirmed by electrocardiograms. The injection in these cases, however, was given very slowly and occasionally it seemed advisable to stop the injection when the patient had received from 800 to 900 c.c. of fluid because he was nauseated or had an uncomfortable feeling in the chest.

In making the glucose solutions only triple distilled water is used, and each new supply of glucose is tested biologically in animals before it is used in any of the solutions. Injection is made at approximately body temperature. These precautions are necessary in order to keep the number of reactions at a minimum.

REPORT OF RESULTS

In the last two years in one of the sections on medicine at the Mayo Clinic twenty-seven patients with asthenic uremia have been treated according to the general plan outlined here. These patients were all extremely ill, and the treatment was intensive;

all received intravenous medication. A brief summary of results is given in Table 1. No cases are included in which the amount of treatment was not sufficient to be of corroborative value. Of the group of twenty-seven cases, nine have been selected to re-

Table 1

Results of treatment in twenty-seven cases of asthenic uremia

Asthenic uremia occurring in	Cases	Improvement						No improvement
		Clinical	In laboratory findings	Clinical and laboratory findings	Temporary	Lasting more than six months	Apparent complete recovery	
Acute nephritis	1	1	1	1		1	1	
Acute exacerbation of chronic nephritis	2	2	2	2		2	0	
Chronic nephritis	24	21	16	15	17	4	0	3

port. In these nine intensive treatment as described was given, and they represent the best results obtained. The reports of the first three cases are somewhat detailed. They represent the possible results of treatment of uremia occurring in three distinct types of renal disease. The other six cases are presented briefly to illustrate treatment and clinical improvement. The laboratory data in the entire group are shown in Table 2, p. 641.

REPORT OF CASES

Case 1.—A man, aged twenty-two, was admitted to the Clinic January 24, 1926, complaining of vomiting and an abdominal pain simulating appendicitis. The onset, three days before, had been gradual; the pain was dull and steady and the vomiting persistent. For two days prior to admission he had passed no urine. He had had a cold since Christmas, and ten days before coming to the Clinic he had developed a sore throat which had been severe for several days, but was not associated with rash of the skin.

The patient's temperature and pulse rate were normal. The leukocytes numbered 13,400; the tonsils were large and infected, the lungs clear; blood pressure was normal; there was no edema, no rigidity of the abdomen and only slight bilateral costovertebral tenderness. A small catheterized specimen of urine was smoky and contained a great deal of albumin, blood, casts, and some pus. The blood urea was 180 mg. for each 100 c.c. A diagnosis was made of acute glomerular nephritis.

Fluids were forced to about 3,000 c.c. daily. Of this amount 1,500 c.c. was given intravenously as 20 per cent glucose in the first two days and 3,000

Table 2

Summary of nine cases of asthenic uremia before and after intravenous treatment

Case	Age, years	Diagnosis	Treatment, days	Blood chemistry: Urea, mg. for each 100 c.c.		Creatinin, mg. for each 100 c.c.		Plasma phosphates, mg. for each 100 c.c.		Carbon dioxid combining power of plasma, per cent by volume		Erythrocytes, millions		Hemoglobin (Dare), per cent		Phenolsulphonephthalein, per cent		Duration of life
				Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	
1	22	Acute glomerular nephritis with uremia	24	240	26	11.0	1.7	9.8	4.3	46	57	3.86	3.49	63	62		70	Living and well, eight months
2	29	Acute exacerbation of chronic glomerular nephritis with uremia	42	400	56	12.0	2.8	8.5	3.5	30	52	1.20	3.48	26	60		25	Living three months, working
3	22	Chronic glomerular nephritis with uremia	24	276	200	13.2	6.7			35	50	1.84	2.56	28	45	?*	10	Living, last report five months
4	15	Acute exacerbation of chronic glomerular nephritis with uremia	34	222	53	17.2	4.0			15	60	2.52	4.30	50	74	?*	20	Fourteen months, felt well six months
5	30	Chronic glomerular nephritis with uremia	6	302	262	21.0	14.5			28	40	2.60	2.65	45	52	?*	?*	Two and one-half months
6	66	Chronic glomerular nephritis and chronic pyelonephritis with uremia	15	291	274	17.0	10.0			15	54	2.25	2.93	40	46			One and one-half months
7	49	Chronic glomerular nephritis with uremia	9	346	217	17.0	10.9	8.7	8.3	64	50	2.54	2.47	36	36			Improving under treatment, developed severe infection and died seven days later
8	31	Chronic glomerular nephritis with uremia	25	246	154	24.0	20.0			39	60	1.60	2.80	26	47	?*	5	Ten months
9	33	Chronic glomerular nephritis with uremia	45	185	146	15.0	12.5					2.13	3.16	43	69	5	5	Four months

*Very faint return

c.c. of Fischer's solution intravenously in the next three days. During the first few days there was marked oliguria almost to the point of anuria. The blood urea rose to 240 mg. for each 100 c.c., and creatinin to 11 mg. for each 100 c.c. Surgical decapsulation was seriously considered, but on the fourth day the patient passed 970 c.c. of urine and rapid improvement followed. Vomiting ceased, pain diminished, and the blood became entirely normal within a week. Tonsillectomy was performed February 12, 1926, and convalescence was normal.

The patient was dismissed from observation February 23, 1926. The chemical constituents of the blood were normal; blood pressure was normal. There was mild secondary anemia, and blood and albumin in the urine. He has been examined several times since his dismissal, the last being July 1, 1926, when the findings were entirely negative except for an occasional red blood cell in the urine. He is at present doing routine work on the farm and feels perfectly normal.

Case 2.—A man, aged twenty-nine, came to the Clinic March 1, 1926, complaining of occipital headaches. His illness had seemed to date from influenza and pneumonia in 1918. Following an acute illness of three months' duration at this time he noticed weakness and the gradual onset of dizzy spells and occipital headaches. In 1924 vision in the left eye was markedly impaired, and in 1925 in both eyes. Gradual improvement followed both of these periods of visual disturbance. The patient had known for two years that his blood pressure was elevated.

Examination revealed a typical picture of rather severe chronic glomerular nephritis. There was moderate secondary anemia, bilateral nephritic retinitis, and a marked degree of peripheral arteriosclerosis, with the systolic blood pressure 200, and the diastolic 140. The blood urea was 88 mg. for each 100 c.c., and blood creatinin 4 mg. for each 100 c.c. A phenolsulphonephthalein test showed only a faint return of the dye in two hours. Urinalysis showed albumin, casts, and red blood cells.

After a period of twenty days in the hospital the patient's condition was definitely improved clinically. Since his tonsils were badly diseased, they were removed March 22. Bleeding occurred in the tonsillar fossa, and a hematoma and cellulitis of the floor of the mouth appeared. The swelling progressed to such a degree that tracheotomy was necessary. All of this occasioned severe acute exacerbation of the chronic nephritis, and the patient became markedly uremic. The blood urea had risen to 400 mg. for each 100 c.c. and creatinin to 12 mg. for each 100 c.c. The leukocytes numbered 30,000, the erythrocytes 1,200,000, and the hemoglobin was 26 per cent. He was vomiting and stuporous, and his muscles twitched. The daily fluid intake was kept at about 2,500 c.c. Of this total amount 1,000 c.c. 10 per cent. glucose was given intravenously daily for the first three days, 1,000 c.c. 20 per cent glucose was given intravenously daily for the next two days, and 500 c.c. Fischer's solution was given daily for the following two days. By this time vomiting had ceased and he was able to continue forced fluids by mouth. He was voiding considerable urine, and all laboratory data indicated improvement. A transfusion of 500 c.c. of citrated blood was

given on the eleventh, fifteenth, and twenty-fifth days. Improvement was rapid and striking. By the thirty-sixth day the erythrocytes numbered 3,480,000, the leukocytes 7,200, and the hemoglobin was 50 per cent. The blood urea was 55 mg. for each 100 c.c., and creatinin 2.8 mg. for each 100 c.c. A phenolsulphonephthalein test showed 20 per cent. return of the dye in two hours.

The blood pressure, which had dropped during the course of the patient's severe illness, had risen again to 190 systolic and 130 diastolic. The tracheotomy wound had entirely closed. He left for home on the forty-second day feeling strong and well. The hemoglobin reading at this time was 60 per cent. When last heard from, three months after leaving the hospital, he was working and doing fairly well, although he still tired easily and complained of headaches and slight weakness.

Case 3.—A man, aged twenty-two, came to the Clinic December 28, 1925, complaining especially of marked weakness. He had had scarlet fever in 1916 and influenza in 1918. In 1922 his application for life insurance had been rejected because of high blood pressure (165 systolic). There were no untoward symptoms until the spring of 1925, when progressive lack of strength and endurance was noted. About November 1, 1925 he had had an unexplained fever and chills for forty-eight hours, some diarrhea, and vomiting. Since then he had failed more rapidly. He began to have headaches, epistaxis, nausea and vomiting, visual disturbances, slight dyspnea, and was very weak.

When examined he was anemic and somewhat stuporous. His breath had a uremic odor. No edema was noted. His heart was enlarged to the left. Systolic blood pressure was 160, and diastolic 92. The fundi showed marked retinitis of nephritis and anemia. The urine contained a slight amount of albumin and the specific gravity was low. A phenolsulphonephthalein test gave only a faint return of the dye in two hours. The blood urea was 276 mg. and blood creatinin 13.2 mg. for each 100 c.c. The hemoglobin (Dare) was 28 per cent; erythrocytes numbered 1,840,000, and leukocytes numbered 5,700. The carbon-dioxid combining power of the plasma was 35 per cent.

A diagnosis of chronic glomerular nephritis with asthenic uremia and severe secondary anemia was made, and the patient was placed in the hospital for treatment. Fluids were forced orally, rectally, and intravenously. The patient was nauseated and large amounts of fluid by mouth caused vomiting. He was given a total daily fluid intake of about 3,500 c.c. The intravenous fluid consisted of 3,800 c.c. of 10 per cent glucose during the first four days. By this time he was no longer nauseated and could retain an adequate amount of fluid by mouth. Transfusions of 500 c.c. of citrated blood were given on the second, seventh, and fifteenth days. Improvement was gradual, but marked. The patient felt stronger and seemed fairly comfortable. He was dismissed from observation on the twenty-fifth day, at which time his hemoglobin was 45 per cent, erythrocytes numbered 2,560,000, the blood urea was 200 mg. and creatinin 6.7 mg. for each 100 c.c., and the carbon-dioxid combining power of the plasma was 45 per cent.

The patient was still living when last heard from five months later, but he was again having considerable trouble.

Case 4.—A boy, aged fifteen, was found to have chronic glomerular nephritis with acute exacerbation due to cervical adenitis and a draining abscess of the right axilla. He was uremic, anemic, and had severe acidosis. He was nauseated, but did not vomit. There was no demonstrable edema.

About 3,000 c.c. of fluids was given daily. Two thousand c.c. of 10 per cent glucose was administered intravenously in the first two days. Three blood transfusions of 500 c.c. each were given. The patient improved (Table 2) and returned home on the thirty-fourth day. He felt well for about six months, when he became more anemic and the blood urea began to rise. He returned for three subsequent examinations, during which time several blood transfusions were given. He lived fourteen months, and then died in uremic coma at his home.

Case 5.—A man, aged thirty, had had chronic glomerular nephritis with uremia and secondary anemia for four years. The onset had been insidious. He was uremic, anemic and dehydrated, and had vomited for several weeks.

The total daily fluids amounted to about 2,500 c.c. One thousand c.c. of 10 per cent. glucose was given intravenously daily during the first three days. Venesection was done for 200 c.c. of blood, and this was followed immediately by a transfusion of 600 c.c. The patient showed definite improvement (Table 2). Vomiting ceased and the output of urine increased. He felt stronger and returned home, where he lived two and one-half months. There was prolonged epistaxis before death.

Case 6.—A man, aged sixty-six, came to the Clinic, where a diagnosis was made of glomerular nephritis, chronic pyelonephritis, renal lithiasis, and uremia. He had failed progressively from renal insufficiency and was in extremis with uremia, anemia, and severe acidosis. He was stuporous, dehydrated, nauseated, and vomiting. His muscles twitched.

About 1,600 c.c. of total daily fluids was given. This included two injections of 20 per cent glucose and 5 per cent sodium bicarbonate (500 c.c. each) the first two days, and then seven daily injections of 500 c.c. of 20 per cent glucose, and two blood transfusions of 500 c.c. each. Vomiting ceased and acidosis was controlled (Table 2). The patient felt stronger and returned home on the fifteenth day. He lived one and one-half months.

Case 7.—A man, aged forty-nine, came to the Clinic complaining of loss of weight, weakness, nausea, and persistent vomiting. Cancer had been suspected. The patient was uremic, anemic, emaciated, and dehydrated. He vomited repeatedly. A diagnosis was made of chronic glomerular nephritis with uremia. The onset had been insidious six or eight months before admittance. The diagnosis was confirmed at necropsy.

About 3,200 c.c. of total daily fluids was given. This included 27 liters of 10 per cent glucose intravenously in sixteen days, and one transfusion

of 500 c.c. of blood. The patient was improving definitely (Table 2). He was feeling stronger and less nauseated. On the ninth day severe parotitis developed, and subsequently cellulitis of the face, otitis media, mastoiditis, and purulent bronchitis. Death followed on the sixteenth day.

Case 8.—A man, aged thirty-two, came to the Clinic because he had failed in health during the last four months. The patient was uremic, anemic, and very weak. There was no edema, nausea, or vomiting. A diagnosis was made of chronic glomerular nephritis with uremia. Apparently he had had mild chronic nephritis for five years.

About 2,500 c.c. of total daily fluids, and two blood transfusions of 350 c.c. and 500 c.c. respectively were given. The patient felt much stronger and returned home on the twenty-fifth day (Table 2). He lived ten months.

Case 9.—A man, aged thirty-three, came to the Clinic because for the last four months he had had definite renal trouble with albuminuria, increased blood pressure, and so forth. For four years he had had slight malaise following influenza. Severe anemia developed gradually and the patient was very weak, uremic, and anemic. There was no edema, nausea, or vomiting. A diagnosis was made of chronic glomerular nephritis with uremia.

Two thousand c.c. of total daily fluids was given. Three hundred fifty c.c. of citrated blood was transfused on one occasion, and on another venesection was done for 200 c.c., and this was followed by transfusion of 600 c.c. of blood. There was definite improvement in general health and in strength (Table 2). The patient returned home on the forty-fifth day and lived four months.

SUMMARY AND CONCLUSIONS

My experience with the intravenous treatment of true uremia and azotemia may be briefly summarized as follows:

1. In certain cases of acute nephritis with uremia the oliguria and toxemia may be controlled with the possibility of ultimate complete recovery.

2. In certain cases of subacute nephritis or acute exacerbation of chronic nephritis with uremia, the severe toxemia may be controlled and the patient tided over the acute stage so that he may live in comparative comfort for some time.

3. In a large group of cases of chronic glomerular nephritis and uremia temporary improvement often occurs. The patients who do not improve are nearly all in extremis when admitted to the hospital. Even in these cases glucose solutions intravenously supply food and fluid, and thus make the end easier.

Hypertonic solutions (usually of glucose), given intravenously, and blood transfusions are rational therapeutic measures, and are of definite value in a certain group of cases of uremia.

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SECONDARY TYPES OF PELLAGRA

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A patient with pellagra always arouses considerable interest in those of us who practice medicine in the Northwest, particularly since patients presenting this syndrome are now observed less often in the so-called nonpellagrous regions. Bender recently called attention to a group of cases in which symptoms of pellagra appeared following organic gastric diseases. The term "secondary pellagra" might aptly be applied to such cases to distinguish them from those in which there are symptoms and signs of pellagra, but no evidence of organic disease in the gastro-intestinal tract. It has been my experience that in most of the sporadic cases of pellagra, of both the primary and secondary types, the patients give a history of having been on a diet containing an overabundance of cereal and an insufficient amount of animal protein, fruits, and vegetables. In the secondary types of the disease this form of diet has practically always been adopted after the onset of gastro-intestinal symptoms and shortly before the appearance of dermatitis.

The term "secondary type" of pellagra must be qualified by an explanation of the secondary cause, such as gastric carcinoma, malfunctioning intestinal anastomosis, stricture of the esophagus, or carcinoma of the rectum. I have observed patients who developed pellagra after adopting a deficiency diet in an effort to reduce weight, and others who dieted in order to improve acne vulgaris, and a still larger group who limited their diet to crackers and toast following operations in the upper abdominal tract, particularly the gallbladder; these types also rightly belong in the secondary group.

Evidence is accumulating which substantiates the observations of Jobling and Arnold that a faulty diet is only one of the

factors that produce the syndrome of pellagra. As they have suggested, the finding of a fungus in the stool from which photodynamic substances may be absorbed from the intestinal tract and circulated in the blood stream, thus hypersensitizing the patient to light and sun rays, is the most recently advocated conception of the etiology of the disease. Jelke has strongly advocated the significance of intestinal parasites in pellagra, but has met with considerable opposition in the South. Goldberger's report on a study of the diet has enlisted many followers, undoubtedly because the correction of a faulty diet has so frequently resulted in cure. The reports have not, however, entirely explained the cause of the disease. It has been suggested that the part the diet plays is its influence on the intestinal protozoa, and not on the patient's cutaneous hypersusceptibility or on toxemia. Parasitologists have called attention to the effects of certain diets on various types of intestinal organisms. The acceptance of this conception of the disease readily explains the infectious and dietetic etiologic theories, which have been widely discussed.

I shall discuss here the histories of five patients who have been examined at the Mayo Clinic during the last five years, and who presented, besides the classical signs and symptoms of pellagra, demonstrable disease of the gastro-intestinal tract which antedated the onset of pellagra. The mechanical interference caused by the various primary lesions are, to me, the predisposing factors in the development of the pellagra in these cases. If the mechanical obstruction is removable the treatment of the pellagra is simplified, but, unfortunately, the general health of many of these patients is so poor because of the primary disease and the pellagra that surgical measures are attended with a high mortality rate.

REPORT OF CASES

Case 1.—A married woman, aged fifty-eight, whose husband has been an invalid for many years, came to the Clinic in March, 1926, because of stomach trouble dating back approximately fifteen years. Gastro-enterostomy had been performed four years previously for "peptic ulcers," and there was complete relief from the gastric complaint until July, 1925, when sudden severe epigastric pain appeared that was only slightly influenced by food.

At times the exacerbations of pain were severe enough to require an opiate. Within the last two months the vomiting had become more frequent, and during the last week practically all food was vomited. Fresh blood in the vomitus and stools had been noted recently. The pain in the epigastrium radiated to the left upper quadrant and to the left scapular region, sometimes so severe as to take away the patient's breath. The patient had not observed jaundice or clay-colored stools. On several occasions the attacks of pain were associated with a chill and slight fever.

On examination the epigastrium was decidedly tender and there seemed to be a mass on palpation. The patient had secondary anemia and was emaciated. A mild dermatitis was noted in the sternoclavicular region and the hands showed several mild patches of eczema. Roentgenograms of the stomach revealed a small ulcer on the lesser curvature and marked deformity of the pyloric end of the stomach due to the former operation. Roentgenograms of the kidneys, ureters, bladder, and gallbladder were negative. The blood urea was 18 mg. for each 100 c.c., the carbon dioxid combining power was 64 per cent by volume, and the blood chlorid 605 mg. for each 100 c.c. No parasites or ova were demonstrated on fresh preparation or on culture of the stools.

At operation the small gastro-enteric anastomosis was disconnected and gastro-enterostomy again performed, because of the finding of a gastric and a gastrojejunal ulcer and a mass in the pylorus, the result of the old healed ulcer. Convalescence was uneventful.

Owing to her husband's invalidism the patient had been the sole support of the small family, and following the operation she continued to subsist on cereals and bread just as she had been doing for the nine months previous to coming to the Clinic. About two months after the second operation her mouth and tongue became sore, and in a few weeks blisters appeared on the backs of the hands and wrists. A recurrence of the patch of eczema was noted on the anterior part of the neck at the same time. She became progressively weaker and mentally depressed.

On the patient's return to the Clinic in the middle of June she was examined in the Section on Dermatology. She was depressed, unresponsive, and emaciated. On the dorsum of both hands and the lower one-third of the wrists was a symmetric reddish-brown, dirty-appearing, thickened, and scaling dermatitis. The borders were erythematous in patches, leaving areas of hyperpigmentation. The anterior part of the neck contained a chronic patch of dermatitis, which was somewhat lichenified with a desquamating and erythematous border to which the term "Casal's collar" has been applied. The tongue was smooth and considerably redder than normal. The neurologic examination was negative. The patient was placed on a diet consisting essentially of milk, fruit juices, green vegetables, yeast, and cod-liver oil, with definite benefit.

Comments.—The differential diagnosis of pellagra from the dermatologic aspect includes erythema multiforme, dermatitis and erythema venenatum (poison ivy, and so forth), erythema

solare (sunburn), squamous eczemas, and lupus erythematosus, particularly of the disseminated types. The absence of the pathognomonic dermatitis of pellagra makes the diagnosis difficult, and to a dermatologist impossible. There are undoubtedly many patients with pellagra sine pellagra, or the constitutional signs of the disease with no dermatitis which go undiagnosed; in fact, such a diagnosis would be possible only by physicians who have had extensive experience with the disease while living in localities where pellagra is endemic. The constitutional signs may sometimes resemble acrodynia, sprue, and syphilis of the nervous system.

Application of the three diagnostic "D's"—dermatitis, diarrhea, and dementia—is often possible in the late stages of the disease. The dermatitis which may be on any part of the body, but more frequently on the exposed areas, as hands, forearms, nose, neck, and lower limbs, is characterized by the dull red pigmentation, the desquamation, the demarcation or well-defined borders, and the hyperkeratosis which gives the dirty appearance. Occasionally there are blisters on the borders of the acute patches of dermatitis.

Diarrhea is often a late complication. In many of the cases I have observed constipation has been marked, even though the stools contained various types of intestinal parasites. The red, beefy tongue and stomatitis are common findings.

Dementia is a late complication and indicates a more serious prognosis. Weakness, mental depression, apathy, paresthesia, neuritis, and later, clinical signs of the degenerative processes going on in the spinal cord, may be manifested.

This patient presents the classical picture of pellagra which was developing as a result of constant vomiting due to a gastrojejunal ulcer and the old malfunctioning gastro-intestinal anastomosis previous to her second operation. There are records in the literature showing that pellagra has been precipitated by surgical operation. In this case there was mild dermatitis on the dorsum of the hands previous to the second operation; this developed into classical pellagra following the patient's dismissal from the hospital. It has been my experience that the secondary

types of pellagra, of which this is a good example, are more fulminating than the primary. Toxemia develops rapidly and is usually severe.

Case 2.—A farmer, aged sixty-three, came to the Clinic because of increasing weakness and stomach trouble which had begun in November, 1925. At the onset of the trouble the abdominal pain, which was confined to the upper left quadrant of the abdomen, was relieved by the use of sodium bicarbonate. The ingestion of food did not influence the discomfort until April, 1926, when the pain became so severe that he only chewed his food and spit it out when well masticated. Milk became the mainstay of the diet. Within the last two months he had been awakened at night by the pain, which had steadily increased in severity; some relief was obtained by vomiting. Blood in the vomitus or tarry stools had not been observed. The patient had been constipated throughout the illness. In May, 1926 dermatitis appeared on the dorsal surface of the hands, wrists, side of neck, and cheeks.

The patient appeared sick and emaciated. There was a partially fixed mass in the epigastrium. On the dorsal surfaces of both hands and the wrists was symmetric and sharply demarcated dermatitis, with erythematous, undermined, pigmented borders, and considerable desquamation. The dirty appearance of the lesion, which is so characteristic of pellagra, was marked. There was evidence of secondary infection in the periphery of the lesions, particularly around the fingers. On the cheeks, nose, and side of the neck were patches of dermatitis of the chronic, pigmented, somewhat keratotic, and dirty type similar to those on the hands. The tongue was glossy, redder than normal, but not painful.

Roentgenograms of the stomach revealed operable gastric carcinoma with marked obstruction. The blood urea was 33 mg. for each 100 c.c., the carbon-dioxid combining power was 24 per cent by volume and the blood chlorids 505 mg. for each 100 c.c. Free hydrochloric acid was absent, a common finding in cases of pellagra and probably the result rather than the cause of the disease. Culture of the stool showed Monilia, but no fluorescent substances.

Abdominal exploration disclosed a large tumor at the pyloric end of the stomach which was attached posteriorly, but not sufficiently to contraindicate its removal. Partial gastrectomy with entero-anastomosis was performed according to the Balfour-Polya technic. About three-fifths of the stomach was removed. No evidence of distant metastasis was noted. The pathologist reported colloid carcinoma and involvement of lymphatic glands.

On the fourth day after the operation uncontrollable diarrhea appeared; this was followed the next day by dementia and wild delirium. The patient died ten days after the operation, exhausted from the uncontrollable delirium.

On examination of the emaciated body the site of the partial gastrectomy and entero-anastomosis was found to be in good condition. The dermatitis of pellagra was noted on hands, face, and neck. The posterior columns of the spinal cord showed degenerative changes and there was marked acute enteritis. There was also evidence of old healed tuberculous pleuritis and

lymphadenitis; hemangioma of the liver; serous atrophy of the heart; arteriosclerotic cysts of the kidney; adenoma of the prostate and generalized arteriosclerosis were also noted at necropsy.

Comment.—The patient complained of mild upper abdominal pain in November, 1925, which became worse in April, 1926, with exacerbations after the ingestion of food. Because of the increased pain the patient did not swallow his food, but chewed it. He drank about a quart of milk a day. In May, one month after starting this habit, dermatitis and glossitis of pellagra developed. He was constipated throughout the greater part of the illness. He was mildly depressed and melancholic. Evidence points to the probability that a patient with operable carcinoma of the stomach and Monilia in the stools developed the syndrome of pellagra when he was forced, because of abdominal pain, to limit his diet practically to milk. Carcinoma had been present for seven months without necessitating a restriction in the diet. However, when necessity forced the patient to eliminate from his diet the bulky foods which have a high vitamin content the signs of pellagra developed within a month. We see many patients each year in the Mayo Clinic with carcinoma of the stomach, but we see relatively few with both pellagra and carcinoma. I believe this may be explained by the fact that the carcinoma acts as a mechanical obstruction and prevents the ingestion of the essential bulky foodstuffs. This limited diet permits of the liberation from the intestinal tract of photodynamic substances which hypersensitize the patient not only to sun but also to daylight. The development of the constitutional symptoms follow as a result of the toxemia. The nature of this photosensitizing substance is not understood; neither are we in a position to explain the mechanism by which the intestinal invaders produce this phenomenon, but it is to be noted that they are frequently present in pellagrins and conspicuously absent in control cases. The hypothesis offered for this case is that the gastric tumor compelled the patient to limit his food to fluids, and because of the existence of the Monilia in the intestinal tract he became hypersensitive to the sun and light and toxemia developed which resulted in death.

Case 3.—A man, aged fifty-five, had been gradually losing weight and strength for eighteen months previous to admission to the Clinic. The use of "tonics" had given him temporary relief on two or three occasions. He had been unable to carry on his work as a railroad mechanic for the last six months and during this time had lost in weight from 218 to 135 pounds. Three months previous to his registration at the Clinic he had complained of gastric distress immediately after eating, particularly in the upper left costal margin. The pain soon became more or less constant and was greatly aggravated by food, so that he limited his diet to bean and potato soup, oatmeal and mush, with a little milk. He had been on this diet for four or five weeks and during this time he had had persistent diarrhea; then dermatitis developed on the hands, neck, and nose.

On examination the patient was pale, emaciated and mentally depressed, had a reddened and glazed tongue, moderate edema of the legs, moderate emphysema of the chest, and severe internal and external hemorrhoids. The rectal shelf was normal on palpation. The abdomen was not distended and there were no palpable masses. A slight tenderness was noted in the left upper quadrant on deep palpation. The neurologic examination was negative. There were acute erythematous desquamating plaques symmetrically distributed on the backs of both hands with slight pigmentation around the borders. The lesions involved the wrists, but did not completely encircle them, a characteristic frequently noted in pellagra. The saddle-like distribution of the keratotic lesions over the nose and the "necklace" dermatitis just above "cupid's bowl" offered a classical example of pellagrous dermatitis. No pulmonary or neurologic signs were elicited. The dermatologist made a diagnosis of pellagra probably secondary to carcinoma of the gastro-intestinal tract and recommended that the roentgen-ray studies include the colon.

Roentgenograms of the stomach, chest, and esophagus were negative, but the descending colon showed a slight filling defect. Occult blood was noted in the stools, but no parasites were found in the one stool examined. The stool was not cultured. Some albumin and hyaline casts were noted in the urine. The hemoglobin was 57 per cent, and the erythrocytes numbered 4,200,000. The blood urea was 24 mg. and the blood sugar 0.12 per cent (Benedict method).

In spite of efforts to increase the vitamin intake the patient rapidly succumbed and died ten days after admission.

At necropsy carcinoma of the descending colon was noted which had perforated and invaded the pelvis of the left kidney. There were also some fatty changes in the liver and evidence of anemia and marked emaciation, dermatitis of the hands, neck and nose, and old healed tuberculous pleuritis and lymphadenitis.

Comment.—The signs of pellagra and the history of prolonged loss of weight and weakness justified a further search for evidence of malignancy. The history was elicited from the patient's family that he had always been a heavy eater and for the first

three months of his illness he had continued to overeat and yet lost weight. This marked loss of weight and strength was associated with practically no abdominal pain at the onset, but later it was associated with pain after eating, a course of events which suggested the possibility of a growing tumor in the gastro-intestinal tract. As the lumen of the bowel became smaller, mild obstructive signs appeared; that is, the pain was aggravated by ingestion of food and frequently caused vomiting. To prevent this discomfort the patient adopted a faulty diet and immediately became rapidly worse.

As would be expected, the dietetic therapeutic efforts in pellagra secondary to carcinoma of the gastro-intestinal tract have been very unsuccessful. Even when the malignant growths have been operable, the toxemia has been so overwhelming that death occurred shortly after removal of the tumors. Efforts to improve the patient's general health previous to operation by increasing the vitamin intake by the use of cod-liver oil, yeast, and green vegetables, have been of material aid in the absence of malignant gastric lesions.

Case 4.—A successful public accountant, aged forty-four, had had stomach trouble off and on for the last fifteen years. Medical measures offered no relief, and in January, 1924, nine months previous to his admission to the Clinic, gastro-enterostomy for duodenal ulcer was performed. The relief from this operation lasted only a month, the symptoms then recurred more intensely than before. A second operation was performed by another surgeon in May of the same year, when "the gastro-enterostomy was repaired" and another opening made in the stomach. The gastric pain almost disappeared following this, but vomiting from one to two hours after each meal continued. In the vomitus was food eaten the day previously. In August diarrhea developed; he passed ten to twelve loose stools a day, and almost simultaneously he noted dermatitis on the back of the hands and forearms. Soreness of the tongue which appeared at this time was thought to be due to the extraction of several teeth. The diet since the second operation had been well mixed and contained the requisite number of calories and vitamins. However, the patient continued to lose weight (28 pounds) owing no doubt to the fact that he was vomiting practically all food.

On examination, on the dorsum of the hands and on the fingers of the first interphalangeal joints, the skin was dry and erythematous with a thickened rough horny layer. The patches were symmetrically distributed on both hands. The periphery contained some vesicles and was slightly undermined. The characteristic hyperpigmentation and the partial encircling of

the wrist were also present. On the forehead and nose were keratotic and pigmented plaques of dermatitis.

Roentgenograms appeared to show two gastro-enterostomy openings, with deformity of the cap. The gastric analysis showed no free hydrochloric acid and the total acidity was very low. *Trichomonas hominis* were in the stool, also *Endamœba histolytica*. A culture for Aspergillus was negative.

Operation disclosed extensive adhesions around the stomach and the upper intestinal tract. There were two gastro-enterostomy openings with a sharp kink of gut between the two. Both anastomoses were cut off and pylorectomy performed because of a hard, indurated duodenal ulcer. No evidence of malignancy was found on section of the ulcer. A temporary jejunostomy was made just below the lowest opening in the jejunum which had been closed, thus permitting feeding by tube. The jejunostomy wound closed spontaneously when the tube was removed three weeks after operation.

Delirium and dementia developed on the third day after the operation and lasted for two weeks. As soon as possible a diet containing fruit juices, cod-liver oil, and yeast was given, and one month after operation forced feedings of green vegetables were also instituted, and the patient rapidly recovered from the mental symptoms. On dismissal six weeks after the operation only residual pigmentation was noted on the hands and face, and moderate edema of the lower extremities was present. He was passing only three or four stools a day. He returned one year after operation in perfect health. He had had a high vitamin diet and arsenical preparations for the endamebiasis. He had regained his former weight and 15 pounds in addition, and had spent the summer in the South, with no signs of the return of the pellagra.

Comment.—The dietetic insufficiency was the result of the constant vomiting, caused by the malfunctioning anastomosis and the duodenal ulcer. This patient is an example of the fact that benign or malignant obstructive lesions in the intestinal tract may produce a picture similar to that produced by pellagra. I have not found that tumors outside of the gastro-intestinal tract lead to the production of this syndrome unless they grew large enough and were so situated as to interfere with the passage or digestion of food in the gastro-intestinal tract.

The significance of the *Endamœba histolytica* and *Trichomonas hominis* in the stools is problematic and will remain so until we learn more about these organisms. The same may be said with regard to the *Lamblia intestinalis* and Monilia in the other cases presented. However, I do not believe we are justified in entirely eliminating these organisms as etiologic factors. The fact that the organisms do not produce local symptoms in the intestinal

tract does not mean that they are not factors in the production of systemic symptoms.

The delirium following surgical interference in these patients presents a serious complication. I have found it advisable in preoperative preparation to institute high vitamin diet, increasing it rather slowly; it is likewise recommended that these patients be kept ambulatory as much as possible. The delirum is the result of toxic psychosis and is impending as a rule prior to operation, so that it readily develops when augmented by the surgical shock. The control and the prevention of this mental complication is a difficult but important phase of the surgery in this group of cases.

Case 5.—A woman, aged thirty-three, while delirious or in an hysteric attack six months prior to admission to the Clinic, drank a concentrated solution of lye. She had had symptoms of psychosis for eight years, and she had threatened suicide for some time. Her diet had been well mixed, and although she had always complained, her husband reported that she ate more than he. There was no history of organic disease. Following the burn from the lye, the patient was dangerously ill for a considerable time, during which rectal feedings and fluids comprised the diet. Stricture of the esophagus followed and was dilated several times by her home physician. The dilatation did not endure, however, and she was compelled to revert to the fluid diet. At times the amount of fluid was small because of the stricture. Dermatitis and severe diarrhea developed three months after the burn.

The patient was emaciated, weighing 66 pounds; her normal weight was 110. She was dull and apathetic and had suicidal tendencies. A wire spiral was passed down the esophagus and met obstruction about 10 inches from the incisor teeth, a second one about 2 inches below. It was impossible to dilate either time because the patient pulled out the thread over which the bougie was to be passed. Three days later a 26 F. bougie was passed through the cicatricial stricture, and three days after that a 29 F. was urged through with considerable bleeding. Roentgen-ray examination of the esophagus was purposely omitted. On the dorsal and ventral surfaces of both hands and half-way up the forearm classic chronic dermatitis of pellagra, in a moderate degree, was noted. On the nose keratotic pigmented and dirty dermatitis was also noted. Peripheral pigmentation was more marked than usual and the erythema conspicuously slight. The tongue was beefy red. Examination of the stool revealed cysts and free forms of *Lamblia intestinalis*. Repeated attempts at forced feeding were fruitless. The patient developed a terminal bronchopneumonia and died.

Necropsy revealed chronic inflammation of the esophagus with scarring and multiple diverticula, an old healed gastric ulcer, advanced emaciation, dermatitis of the hands and face, and terminal bronchopneumonia.

Comment.—I have had the opportunity to observe patients with various forms of psychosis who refused food, and later developed pellagra. Attempts at rectal feedings have been unsuccessful and the patients have died. This woman had a manic-depressive type of psychosis dating back eight years, or to the time of her marriage. Her mother had been an inmate in a hospital for the insane on several occasions. The esophageal burn followed by the scarring of the esophagus was the mechanical factor that interfered with the intake of food.

The degree or the extent of the dermatitis does not always indicate the severity of the toxemia. The dermatitis in this case was mild. However, the toxemia of the pellagra augmented by the psychosis became uncontrollable and prevented therapeutic efforts. Hence, the extent of the dermatitis or its status may not be of prognostic value, although it may be an important diagnostic sign.

SUMMARY

The histories of five patients are presented who had pellagra besides an organic lesion in the gastro-intestinal tract which prevented them from ingesting mixed food or of retaining food in the stomach. The term "secondary pellagra" has been suggested for this syndrome, and I have recommended qualifying it by denoting the type and situation of the lesion causing the mechanical interference. It would seem that these five cases add further weight to the fact that deficient diets or unassimilated well-mixed diets are a factor in the production of pellagra. In the secondary group the faulty diets are the result of demonstrable mechanical interference, while in the primary types of the disease the diet is selected by the patient because of gastro-intestinal symptoms for which we find no demonstrable cause other than the intestinal parasites. The symptoms of dermatitis, toxemia with degenerative processes, and gastro-intestinal symptoms are probably not attributable to diet deficiency alone, but are evidences of some other pathologic processes. It is with the hope of isolating the cause of these significant processes that attention has again been directed toward the study of the stools. Isolating various parasites from the stools and interpreting their local and systemic

significance will require prolonged and intensive study. We have isolated, in a high percentage of cases, organisms of various types from the intestinal tracts of patients showing various phases of cutaneous photosensitiveness, and have found but a very small percentage of positive stool cultures in the asymptomatic control cases studied, but we have not progressed beyond this point. It is necessary now to show that in patients with amebiasis, pellagra may more easily be produced with a deficient diet than in those whose stool examinations are repeatedly negative. At the same time it is essential that the parasitologist shall crystallize our knowledge of the pathogenicity of the various types of intestinal organisms, estimating not only the types that produce symptoms in the intestinal tract but also determining the influence the various ameba may exert elsewhere in the human organism.

The indication for this report is warranted by the fact that the removal of the obstructive lesions in the gastro-intestinal tract if recognized early in the course of pellagra will permit its rapid cure. Also, the recognition of the secondary type of pellagra indicates the presence of a lesion, either benign or malignant, which interferes with the passage or digestion of food somewhere along the gastro-intestinal tract.

CUTANEOUS LESIONS DIAGNOSTIC OF CONSTITUTIONAL COMPLAINTS

WILLIAM H. GOECKERMAN

It is a regrettable fact that the etiology of many cutaneous diseases still remains obscure. However, the dermatologist has known for many years that lesions of the skin are frequently the symptoms of well-recognized systemic disturbances. In some of these cases the lesions of the skin are the only tangible expression of disease, in others the lesions are associated with symptoms referable to other structures of the body, and in such instances they may prove diagnostic of disease whose other manifestations are exceedingly puzzling. The cases reported here are illustrative of this valuable feature of dermatology which is too often ignored.

REPORT OF CASES

Case 1.—A man, aged forty-eight, was first seen in the Clinic in January, 1918. He was then complaining of pain and stiffness of the left shoulder. After this he fell from a wagon, fracturing the left clavicle and injuring the shoulder. The clavicle healed uneventfully under immobilization, but the shoulder remained stiff. Massage with liniment, baking, and even forcible manipulation of the joint under ether were of no benefit.

The patient was seen in the Section on Dermatology in July, six months after the accident. At this time there were lesions about 3 cm. in diameter on the forearms just above the wrist. The patient did not attach any importance to these lesions; he explained them as due to chafing from friction by a shirtcuff. At a former examination areas of chronic irritation had been noted on the arms. Careful inspection showed that the elementary lesions in the patches were small, indurated nodules arranged in an arciform configuration. Associated with this was moderate scaling, crusting, and definite atrophic scarring. These criteria readily stamped the lesions as a nodular tertiary syphilid. The Wassermann test on the blood was negative, but under provocative arsphenamin injection three positive tests out of a total of six were obtained. Under treatment for syphilis the lesions healed rapidly and the shoulder improved gradually, so that the patient was able to return to work in six weeks after treatment was begun. He had been married for fourteen years; his wife had not had any miscarriages and had

borne two healthy children, one of whom died when nine days old. The patient denied knowledge of venereal infection.

Comment.—There was little to arouse the examiners' suspicion that the persistent complaint with regard to the shoulder might be of syphilitic origin. The history did not point to this disease and a routine Wassermann examination was negative. Yet a careful examination of seemingly unimportant lesions of the skin definitely showed the presence of the infection, which in this instance proved to be the chief cause of the complaint.

Case 2.—A man, aged thirty-three, was examined in the Clinic April 1, 1918. He complained chiefly of abdominal pain and fever. An eruption on the face and neck was diagnosed lupus erythematosus with chronic and acute lesions. While the examiners were aware that lupus erythematosus may be associated with systemic symptoms such as this patient complained of, an exploratory abdominal operation was finally decided on. The exploration revealed nothing in the abdomen to account for the trouble. At necropsy extensive tuberculous involvement of the mediastinal retroperitoneal and pelvic lymph nodes was noted. The spleen and left lung were also tuberculous.

Comment.—This case is a striking illustration of the association of systemic complaints with disseminate lupus erythematosus. In this instance the eruption was not considered sufficient to explain the complaint. But it should be emphasized that the etiologic background of lupus erythematosus, especially when it shows a tendency to disseminate, is commonly accompanied by complaints other than those referable to the skin.[1] These complaints vary markedly. Usually the patient has complained of lack of physical endurance for years before the cutaneous lesions appear. Irritability and sensitiveness are out of proportion to the apparent physical ailments. Vague abdominal pains, at times severe, are almost always referred to. Common also are aches and pains in the joints. There may be moderate to marked elevation of temperature for a long time, or there may be sharp hyperpyrexial attacks. Frequently the urine contains moderate to large amounts of albumin. Manifestly this is not a clear-cut syndrome in the absence of lesions of the skin, but even when these are present they are not always as characteristic as they were in

this case. Often such lesions as are present are not particularly conspicuous and are, therefore, ignored as being of no diagnostic value. It cannot be too forcibly emphasized that in an obscure case all cutaneous lesions, no matter how insignificant, should be carefully studied in order that they may serve as aids in diagnosis. In disseminate lupus erythematosus, for instance, the "butterfly" configuration is of secondary importance. Frequently such distribution is not in evidence. The face and scalp must be scrutinized for signs of old lesions, atrophy, and patches of alopecia. The face must be studied for a persistent flush; the lips for silvering; the mucous membranes for erosions; the skin of the upper trunk, neck, and extremities for signs of old lesions; and the ears, fingers, and toes for bluish, chilblain-like papules and patches. Occasionally, especially when the eruption is more pronounced, seborrheic or eczematoid dermatitis, erythema multiforme, dermatitis venenata, the sarcoids, lichen planus, erysipelas, and pellagra may be more or less closely simulated. In all such cases, if the eruption is correctly interpreted, the constitutional complaints are usually readily explained.

Case 3.—A woman, aged thirty-one, was first seen in May, 1920. She complained of irritation in the throat with cough and moderate expectoration. Aside from this she felt very well and her weight was about 12 pounds above average.

Routine physical examination showed some bulging of the right posterior wall of the chest, but the lungs appeared to be normal. An eruption on the upper part of the back, the buttocks, and the right upper arm was thought to be eczema. Examination of the sputum showed bacilli of tuberculosis. The patient was then seen in the Section on Dermatology and the eruption was pronounced lichen scrofulosorum. Subsequently roentgen-ray examination of the lung disclosed an area of infiltration in the left second interspace, about 3 cm. in diameter, which was believed to be an abscess. Because of the presence of bacilli of tuberculosis in the sputum, the lichen scrofulosorum and the shadow shown by the roentgen ray, the chest was given further careful clinical study for a few days. The final diagnosis was thick-walled tuberculous cavity of the upper lobe of the left lung.

Comment.—The lichen scrofulosorum was not the only sign pointing to tuberculosis in this case. It was, however, valuable confirmatory evidence. Certainly a correct interpretation of the lesions of the skin guaranteed their intelligent management. If

the condition had been looked on as eczema the treatment would probably have been disappointing. The lichen scrofulosorum was somewhat unusual in this case, since such an eruption is more frequently seen in children and adolescents. It is also much more commonly associated with glandular than with pulmonary tuberculosis. It is very likely that this patient may have tuberberculosis of the deeper glands, even if they were not demonstrated clinically. Glandular tuberculosis is so protean and often so puzzling in its manifestations that an eruption in the form of lichen scrofulosorum or one of the other tuberculids may prove of inestimable diagnostic value. This is true also of some of the obscure complaints found in childhood.

Case 4.—A man, aged thirty, was seen for the first time in December, 1921. He complained of a dull ache in the upper abdomen and various gastrointestinal disturbances. On palpation there was some tenderness in the epigastrium and right hypochondrium, but no palpable masses. He had lost about 20 pounds in weight. Roentgen-ray examination of the stomach and colon did not reveal any abnormality. The skin was noted as being dry and pigmented, especially in the axillæ, around the nipples, and over the abdomen. The patient said this had always been so. The remainder of the examination revealed nothing of importance, except possibly moderate-sized hemorrhoids. It was decided that the symptoms were chiefly functional.

The patient was again seen by his former examiner in April, 1922. His complaints were similar to those on his previous visit, but definitely more pronounced. Enlargement of the liver and a firm nodule in the right epigastrium were also noted at this examination. The pigmentation had increased and the leukocyte count was 30,400. He was seen by the dermatologist, who promptly made a diagnosis of acanthosis nigricans. The correct interpretation of the cutaneous lesions drew attention to the probability of abdominal malignancy. This suspicion was confirmed by the excision and microscopic examination of a nodule from the liver which proved to be adenocarcinoma.

Comment.—Acanthosis nigricans, when developing in an adult, practically always points to abdominal malignancy. When fully developed it presents a characteristic skin picture (Figs. 84–86).

CONCLUSIONS

The cases presented here illustrate the value of the correct interpretation of any lesions of the skin, since they are often of

Fig. 84.—Characteristic distribution of pigmentation and hyperkeratosis. Sometimes these regions show special features before they can be found on any other part of the body.

Fig. 85.—Papillary growths, a feature of acanthosis nigricans.

definite diagnostic aid by helping to account for obscure constitutional symptoms. To call a syphilid dermatitis, or a tuberculid acne shows careless disregard for the true diagnostic value of the lesions of the skin. Examples illustrating this feature of dermatology could be multiplied endlessly. I have

Fig. 86.—Hyperkeratosis.

chosen a few in which its value seemed beyond cavil. When the diagnostician is confronted with a patient complaining of obscure constitutional symptoms he should not rest satisfied until all possible cutaneous lesions have been carefully differentiated.

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FIBROSARCOMA OF THE MALE BREAST

HAROLD D. CAYLOR AND JOHN J. SHUGRUE

Connell, in 1907, reviewed the literature and found that only thirty-four cases of various types of sarcoma of the breast of men had been reported. Carcinoma is the most common malignant growth in the male breast, and sarcoma is next in frequency,[1, 3, 9] fibrosarcomas forming by far the largest group, twelve in twenty-six cases. Many authors believe that this type of malignant neoplasm frequently arises in fibro-epithelial tumor (fibro-adenoma, adenofibroma).[5, 6, 7, 8, 9]

Fibro-epithelial tumors may be present in persons at any age, usually after puberty, in both sexes. They constitute approximately 17 per cent of all mammary tumors and about 2 per cent occur in males.[3] No more is known of their etiology than of any other benign tumors. Fibro-adenomas usually persist for a long time as slow-growing, hard, slightly nodular, freely movable lumps in the breast, usually in the upper quadrant. The next most common site for their appearance is behind the nipple.[3] They are composed of irregular interlacing whorls of fibrous connective tissue, and scattered throughout this stroma are irregular epithelial-lined cysts and strands of epithelial cells. Edematous, myxomatous, and cystic changes are sometimes found. Rapid alteration of the size or texture of the growth may herald a malignant change. Speese mentioned a case of fibrosarcoma developing from a nodule which had been present in a man's breast for twenty-two years.

The average age of men when sarcoma of the breast develops is forty-five and six-tenths years, according to Finsterer, and for carcinoma, fifty-five years. In a series of twenty cases of sarcoma of the male breast Connell found that four patients were between the ages of twenty and twenty-five years, and five were

between fifty and fifty-five. The oldest man in the group was aged seventy-three. Trauma was not important as an etiologic factor. A family history of malignancy of the male breast was noted in two instances. Connell reported eleven cures in thirty-four cases of all kinds of sarcoma of the breast in men. Finsterer, in 1906, reported only one cure in twelve cases.

Fibrosarcomas are usually firm and nodular, attached more or less to the adjacent structures, and late in the course of the disease to the skin. They were most frequently situated in the upper quadrants of the breast. Grossly they often closely resemble edematous fibro-adenomas.[5]

REPORT OF CASE

A man, aged fifty-two, came to the Mayo Clinic complaining of a "lump" in the upper outer quadrant of the left breast which had been present for about twenty years. Except for typhoid fever and tonsillitis in youth his

Fig. 87.—Cut surfaces of the tumor.

history was negative. When first noticed the mass was about 2 cm. in diameter, and it remained about this size. The patient had been severely burned by roentgen-ray treatment for the tumor about eighteen years previously. Direct pressure on the tumor caused discomfort, but unless the tumor was manipulated the patient was unaware of its presence. During the six months

before he came for examination the tumor grew to about three times its former size.

The only discomfort complained of during the physical examination was pain when the arm and shoulder were moved or when direct pressure was applied to the tumor by the examiner's fingers. The patient's appetite was good; his weight was stationary, but he had lost some strength. The skin over the firm, hard, irregular mass was fixed to it; it was stretched, atrophic, discolored brownish red, and scarred, probably from the old actinic dermatitis. A few small lymph nodes were palpable in the left axilla. Roentgen-ray examination of the chest did not reveal metastasis.

A clinical diagnosis of cancer of the breast was made and a radical amputation was performed through a modified Stewart incision. The growth, which was very vascular, was 6 by 5 by 4 cm. in its greatest dimensions. It

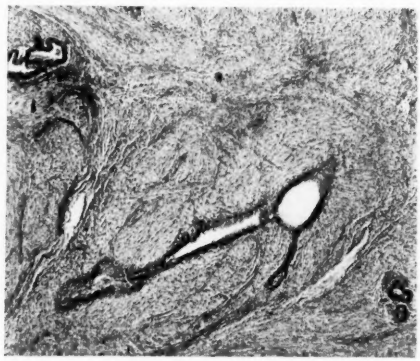

Fig. 88.—Connective-tissue stroma with strands and small cavities lined by epithelial cells typical of fibro-adenoma (× 30).

was firm and lobulated, and in a few areas fibrous tissue was invading the adjacent fat (Fig. 87). The cut surfaces were dirty gray and white stippled with a few small old and recent hemorrhagic areas.

Microscopic examinations of different parts of the tumor revealed three types of structure. In one section fibrous connective tissue predominated. Irregular cords and spaces lined by epithelial cells were intermingled in the stroma, which is typical of a fibro-adenoma (Fig. 88). In another section, which was a modification of the first, the connective tissue in most areas was myxomatous (Fig. 89). Sections from the third area of the tumor were much more cellular than those described, and mitotic figures were found in many fields interspersed with spindle-shaped malignant cells of fibrosarcoma (Fig. 90). The pathologic diagnosis was fibromyxosarcoma, grade 1, in a fibro-adenoma. The axillary lymph nodes were not affected by the malignant neoplasm.

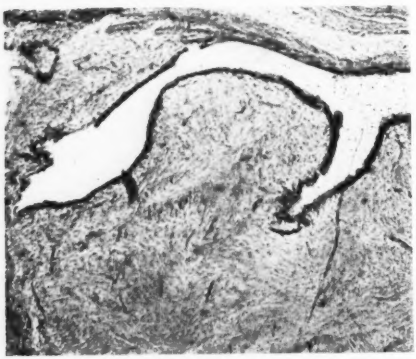

Fig. 89.—Area of the fibro-adenoma illustrating the myxomatous change (× 30).

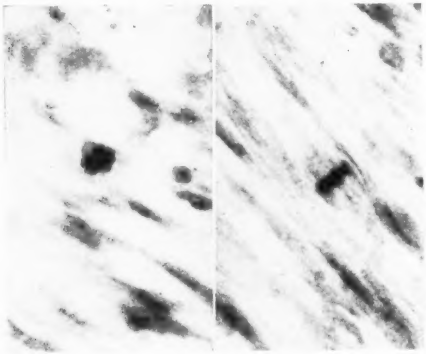

Fig. 90.—Mitotic figures in the nuclei in cells of the fibrosarcoma (× 500).

COMMENT

This case had some of the cardinal points often noticed when fibrosarcomas develop in fibro-adenomas. We have recently seen a similar tumor in the breast of a young woman. It likewise was of a low grade of malignancy. The case illustrates the salient points frequently seen in cases of sarcoma of the male breast. It also illustrates the need of careful study for malignant change of many areas of an apparently "innocent" tumor.

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EXTRA-UTERINE PREGNANCY; PAROVARIAN CYST; SOLID CARCINOMA OF THE OVARY; ADENOMYOMA OF THE UMBILICUS

LEDA J. STACY, DELLA G. DRIPS, SUSAN R. OFFUTT, AND L. MARY MOENCH

EXTRA-UTERINE PREGNANCY

Case 1.—A married woman, aged thirty-eight, came to the Clinic with a history of having had one miscarriage sixteen years previously, of menstrual periods that were regular and without pain until two months before her examination, and an attack of severe general abdominal cramping, rather more severe in left lower quadrant radiating into chest and requiring a hypodermic of morphin, seven weeks before. Nausea and vomiting accompanied the pain. She had a second similar attack two weeks later and flowed with each attack. During the attacks micturition was scant and painful and defecation was painful. Subsequently the patient had had three other attacks, although the pain was less severe and more localized in the right lower quadrant. There was no fever.

Examination revealed a small tender mass behindand to the right of the uterus. The urinalysis and roentgenograms of the kidney, ureter, and bladder were negative. A diagnosis was made of probable ectopic pregnancy and operation advised. At operation extra-uterine pregnancy of the right tube was found. The external third of the tube had ruptured and the appendix was secondarily involved. The tube and the appendix were removed.

The patient recovered uneventfully and was well for five months, when she returned to hospital in considerable pain. She had been entirely well until two weeks previously, when, following a scant menstrual period which was two weeks early and lasted only two days, she had had a severe cramp-like pain in epigastrium radiating to left lower quadrant, where there was some tenderness. The following day another similar attack occurred and again on the fourth and eighth days. The attacks were repeated with increasing weakness until she was admitted to the hospital.

Examination disclosed a tender mass in the left side of the pelvis and a diagnosis of ectopic pregnancy was made. At the operation extra-uterine pregnancy in the left pelvis and a large hematoma were found. Rupture had occurred at about the seventh week.

Comment.—The history in this case is fairly typical of extrauterine pregnancy, but is unusual because of the second pregnancy in less than five months after the first. The long interval between the miscarriage and the first ectopic pregnancy is not of significance, for the patient had been a widow for a number of years and had married the second time a year and a half previously. Farrar reports four cases of second ectopic pregnancy in a series of 186 cases. We have seen two patients within the last year who had been operated on for ectopic pregnancy and because of apparent repetition of the symptoms made their own diagnosis of ectopic pregnancy and came for operation. Examination of the pelvis of one of these patients did not reveal a pelvic mass and her symptoms subsided while she was under observation. The other patient had a tender, soft small mass in the left adnexal region and a diagnosis of probable ectopic pregnancy was made, but operation disclosed a hemorrhagic ovarian cyst.

Case 2.—A married woman, aged forty-one, was first seen July 10, 1926. Her chief complaint was low bilateral abdominal pain of six weeks' duration. The pain was expulsive and she said it felt as if "something were pushing things forward." Defecation was accompanied by such acute abdominal pain that she would scream. Bowels were regular and there was no diarrhea, but some blood followed the stool. The last pregnancy was eleven years ago and there had been no previous pelvic operation. Menstruation for the last five years had been irregular at intervals, often appearing every two weeks. The last two months the periods had been unusually regular for her; the April, May, and June periods had been exactly twenty-one days apart and were normal in amount and with no more than the usual discomfort. The last period was eight days before the present examination. For the last six months there had been a pinkish tinge to the leukorrheal discharge, but no definite spotting. She had experienced slight nausea but no vomiting.

There was a very tender mass in the posterior culdesac and a small tender mass in the region of the right tube. There was less tenderness in the left adnexal region. The fundus uteri was anterior and movable, and normal in size and the cervix was slightly soft. The hemoglobin was 74 per cent. Ectopic pregnancy was diagnosed. Operation revealed right tubal pregnancy and pelvic hematoma. The right tube and appendix were removed and a small uterine fibromyoma excised. Convalescence was uneventful and the symptoms that preceded operation were relieved.

Case 3.—A married woman, aged thirty-three, registered February 20, 1926, complaining of pelvic pain and profuse vaginal bleeding. In January, 1925 she had given birth to a normal full-term child in breech presentation.

November 23 menstruation was reëstablished with a normal period lasting four days. This was followed in December by what seemed a scant normal period, but on the third day severe cramp-like pelvic pain appeared and continued at intervals for three weeks. The uterine bleeding persisted during this time and required three napkins daily. The pelvis was then examined and the uterus found about normal in size. No mass was detected, but the cervix was soft and enlarged, with some mucosanguineous discharge from the external os. The symptoms continued for ten days following this examination and curetment was done. Symptoms were relieved for three days, when severe pain was felt in the left side of the pelvis and the temperature rose to 101°. The patient was kept in bed for several days until the fever subsided and her general condition permitted her to travel. She reported at the Clinic February 20.

The general physical examination was essentially negative. The perineum was moderately lacerated and the cervix large and soft. A firm mass, fixed and slightly tender, was felt in the posterior portion of the pelvis with a free margin shelving to the right. The uterus was normal in size and consistency. At this time the temperature was normal. There was secondary anemia with 62 per cent hemoglobin (Dare); the erythrocytes numbered 3,700,000, the leukocytes 10,000 and 7,000 on two readings, and the differential count was normal. Inasmuch as the bleeding had ceased and in view of the history of recent pyrexia the patient was admitted to hospital for observation. Slow hot douches were instituted with ice to the abdomen, and as several days passed without rise in temperature, it was thought advisable to explore the abdomen March 4. Extra-uterine pregnancy was found in the right tube which was lying across the pelvis forming a mass about 5 cm. in diameter. The pelvis was otherwise negative.

Comment on Cases 1, 2, and 3.—The articles on extra-uterine pregnancy in text-books on gynecology would lead one to believe that in most such cases there is a classical history of vaginal bleeding associated with sudden severe pelvic pain and collapse after one or two months of amenorrhea.

Probably in less than 50 per cent of cases of extra-uterine pregnancy is there a history of a missed period. The usual history is that of one or two weeks' delay in the appearance of menstruation, or there may be no irregularity in the menstruation, as in Case 2; but the flow does not cease as it normally should and metrorrhagia persists with more pain than is usually experienced during menstruation, the pain localizing in either tubal region. It is not until there is some separation of the decidual membrane from the endometrium that uterine bleeding occurs. Pain is the predominant symptom, but usually does not occur

until the ovum dies and becomes a foreign body which the tube attempts to expel; it becomes a more constant symptom when rupture takes place with hemorrhage into the peritoneal cavity. It is then that painful defecation becomes a prominent characteristic symptom of extra-uterine pregnancy, and vaginal and rectal examination reveals a tender mass in the culdesac. In these cases the softening of the uterus and cervix, and the enlargement of the uterus and other signs of pregnancy may be too indefinite to be of importance in differential diagnosis, although they may be at least suggestive. Miscarriage is most often confused with ruptured extra-uterine pregnancy and many patients give the history of curetment for supposed miscarriage without control of symptoms, as cited in Case. 3. A carefully elicited history and thorough vaginal and rectal examination usually prevent this error.

An ovarian cyst with twisted pedicle may produce similar symptoms, but the accompanying signs of pregnancy are absent. Since operation is indicated in both conditions, differential diagnosis is not so important to the patient.

A retention cyst of the ovary or a hemorrhage into a cyst may be difficult to distinguish from early extra-uterine pregnancy, but a short time of observation usually enables one to establish the diagnosis.

Acute salpingitis, acute appendicitis, and renal colic may produce a similar type of pain and in much the same area, but the accompanying symptoms and signs are sufficiently characteristic of the respective lesions to make the differential diagnosis fairly clear.

PAROVARIAN CYST

Case 4.—A woman, aged thirty-five, came to the Clinic October 15, 1925, complaining of enlargement of the abdomen which had been present since March, 1918. In May, 1917 she had given birth to a full-term anencephalous fetus. The following January seven or eight attacks of severe pain in the left lower abdomen during a period of three weeks had been followed by a continuous dull pain in this region and a gradual increase in the size of the abdomen. This enlargement, associated with nausea and vomiting, was at first thought to be the result of pregnancy, but, as the size of the abdomen increased very rapidly, ascites was diagnosed. In 1918 the patient became pregnant and in April, 1919 gave birth to a normal child. The fol-

lowing year a second pregnancy occurred in spite of the persisting "ascites" and at four months aspiration was necessary. Three gallons of clear fluid were withdrawn. A normal child was born in November. Subsequently large quantities of fluid, described by the physician as being "as clear and sparkling as water from a spring," were withdrawn at intervals during the following year. A third normal child was born in April, 1924, and soon after this aspiration was again necessary. During the next year and a half the patient was greatly inconvenienced by the size of the abdomen and decided to come to the Clinic for relief if possible from this condition.

When she was examined her excellent general condition seemed to preclude the possibility of tuberculous ascites of the duration described, and no local or general cause for ascites could be determined. Because of the distention of the abdomen it was impossible to outline the pelvic structures. However, in view of the history of an onset characterized by attacks of pelvic pain and the description of the fluid aspirated as "clear and sparkling," a diagnosis of parovarian cyst was made. Abdominal exploration was therefore performed and a large parovarian cyst filling the entire abdomen was found. The ovary was flattened out on its surface.

Comment.—Large parovarian cysts are often difficult to distinguish from ascites and their presence is difficult to detect in very obese patients. Parovarian cysts are thin walled, usually only partially filled with fluid, therefore not presenting a definitely outlined tumor or a sense of tension or ballottement to the examining hand. Percussion dulness may vary with the change in the patient's position as it does in the presence of free fluid, but the tympany of the colon usually may be elicited in the upper part of the abdomen above the level of the dulness over the tumor. The pelvic examination gives little aid in diagnosis, as the tumor is often entirely abdominal. Although parovarian cysts develop within the broad ligaments, they may become pedunculated and subject to torsion, and it is probable that such was the case in the early history as given. The aspiration of clear fluid is pathognomonic of parovarian cyst.

SOLID CARCINOMA OF THE OVARY

Case 5.—A woman, aged twenty-five, registered at the Clinic January 19, 1926, complaining chiefly of vaginal bleeding. The family history was of no interest. She had been married a few years previously, lived with her husband six months, and had had one miscarriage at three months. The menstrual periods had been somewhat irregular from puberty. This condition together with long-continued discomfort in the lower right abdominal

quadrant led to an exploratory operation July, 1924, at which time the appendix and right ovary and tube were removed. The left ovary and tube were said to have been normal at this time. After this operation the menstrual periods were much more irregular, and appeared only every three or four months. The flow lasted three or four weeks. It had been constant for three months before the admission of the patient, who was then weak and dyspneic on exertion. She had had no pain, but complained of a low backache which also had been constant for several months. She said her home physician had discovered a pelvic tumor on examination in July, 1925. He had advised panhysterectomy which she wished to avoid.

The general physical examination, aside from definite pallor of the mucous membrane and some indefinite lower abdominal tenderness, was essentially negative. Pelvic examination revealed a brawny infiltration filling the culdesac and extending laterally into both sides of the pelvis. No pelvic structures could be outlined. A tentative diagnosis of pelvic inflammatory disease was made and the patient was sent into the hospital for the usual treatment of hot packs and hot douches. There was no fever. The leukocytes numbered 9,000, the erythrocytes 3,800,000, and the hemoglobin was 44 per cent. The blood Wassermann test was negative.

January 29, one week after admission to hospital, a pelvic examination revealed considerable change. It was possible to outline the uterus of apparently normal size anteriorly and to the right. There was still the large firm, infiltrating mass filling the posterior portion of the pelvis and impinging on the rectal lumen. By February 8 there was still more improvement. The uterus had become movable, and a smooth rounded, very hard tumor could be outlined, filling the posterior part of the pelvis.

Infected ovarian tumor was diagnosed and a pelvic exploration advised. The patient was operated on February 10. An ovarian tumor about 7 cm. in diameter was removed first. Left salpingectomy was also performed for infected hydrosalpinx. The ovarian tumor was immediately reported by the pathologist to be malignant, whereupon the surgeon proceeded to remove the uterus and remainder of the ovarian tissue on the left side. The right ovary and tube had been previously removed. The pathologic report on the ovarian tumor was solid carcinoma showing malignancy grade 3.

Comment.—In this case, because of the age of the patient, malignancy was not suspected. The symptoms were unusual. Bleeding was the one cardinal symptom. The absence of pain which is considered as the most frequent initial symptom of malignant disease of the ovary was unusual. The secondary inflammatory infiltration obscured the true pathologic condition so that on first examination the diagnosis was pelvic inflammatory disease. Fortunately, direct observation and treatment permitted a more correct diagnosis as the inflammatory exudate became absorbed.

ADENOMYOMA OF THE UMBILICUS

Case 6.—A negro woman, aged thirty-nine, registered at the Clinic in March, 1926. She knew nothing of her family history. She had never been pregnant. Her chief complaint was a gradual increase in the size of the abdomen of which she had been conscious for three years. She associated this with the uterus because of the increase in the amount and duration of the menstrual flow. For one year there had been much soreness and pain in the lower abdomen which seemed to center about the umbilicus. This soreness and pain were much intensified at the time of the menses and she insisted there was a small growth in the navel from which menstruation had occurred at the regular period on four different occasions during the past year. She thought she had lost 2 or 3 drams of blood from the umbilicus at each menstruation. She had noted no leukorrhea or intermenstrual vaginal bleeding.

On examination of the abdomen, a large mass which filled the median lower part of the abdomen and reached to the umbilicus was easily outlined. It was firm and irregular and felt like an enlarged irregular body of the uterus. A small irregular, very tender mass was palpated beneath the umbilicus. It was attached to the larger tumor below and also to the overlying skin of the umbilicus. A small purplish nodule could be seen in the umbilicus. Pelvic examination confirmed the impression that the tumor filling the lower abdomen was an enlarged uterus containing multiple fibromyomas. The hemoglobin was 42 per cent; otherwise there was nothing of note about the physical findings or laboratory tests.

The patient was sent to the hospital with a diagnosis of multiple fibromyomas of the uterus and adenomyoma of the umbilicus. At operation, March 17, multiple fibromyomas of the uterus were found, making a mass the size of a seven-months' pregnancy. Some of these were degenerating and had become adherent in the pelvis. A small tumor at the umbilicus was excised, which was found to be an adenomyoma on microscopic examination. Total abdominal hysterectomy was performed with removal of both tubes and ovaries and the patient has recovered uneventfully.

Comment.—This case seemed worthy of note because of the comparative rarity of adenomyoma of the umbilicus and because it gives an opportunity to call attention again to the associated clinical symptoms.

Cullen, in 1916, had reviewed in the literature and from his personal experience about a dozen cases of adenomyoma of the umbilicus. Judd and Foulds in 1923 reported 494 cases in which adenomyoma was found at operation; only one of these was at the umbilicus. Cullen, who was among the first to call attention to this tumor, described it as "occurring in the umbilical cicatrix of women between the ages of thirty-five and forty-five, reaching its full development within a few months

after its appearance, and characterized clinically by redness, swelling, pain, and in some instances, bleeding from the tumor at the menstrual periods."

An area of pigmentation over the tumor has been noted by certain observers. The tumor is usually attached to the skin and underlying structures. When there is no frank bleeding from the growth at the menses there is often a chocolate-colored discharge. The growths are usually associated with benign pelvic tumors.

PREGNANCY AND DIABETES

ELOISE PARSONS, LAWRENCE M. RANDALL, AND RUSSELL M. WILDER

Women with diabetes do not usually become pregnant. Our records since 1922 contain but eleven instances among 285 women of the child-bearing age; Joslin encountered only eleven instances in his large practice, and von Noorden only twenty-two among 427 women. Reasons for this are apparent. Amenorrhea is so common as to be the rule in incompletely controlled severe diabetes, and sterility in such cases may be presumed to be due to failure of ovulation. Young diabetic men are often impotent, and in them atrophy of the testicles has been demonstrated (Naunyn). Similar atrophy of the ovaries in women may be expected. But even if the menses are uninterrupted fertilization may be prevented by the abnormal secretions resulting from vulvitis, vaginitis, and cervicitis. And, finally, in many cases conception is avoided by intent, such action being prompted by the patient's or her medical advisor's fear that pregnancy will be badly borne.

The danger of pregnancy to diabetic women has been considered to be very grave and diabetes has been regarded as an indication for therapeutic abortion. Williams and Offergeld have reported that from 25 to 30 per cent of such patients died in coma at delivery or shortly after; others died from infection to which they were predisopsed by their disease; and others died because the relatively mild diabetes became aggravated during pregnancy. The prognosis from the standpoint of the child was equally ominous. Abortions and stillbirths were much more common than living children. In our series of eleven patients, one with very mild diabetes of seventeen years' duration had three pregnancies and three children. The pregnancies of the other ten women resulted in five children, two stillbirths, and four miscarriages.

It is doubtful whether patients with severe diabetes ever survived pregnancy in the pre-insulin era. Of our eleven patients, all but two had mild diabetes; these two, whose conditions are to be described, had the benefit of insulin. Joslin's successful cases (Cases 436 and 1207) were of moderate severity. The woman in Case 436 was an obese Jewess who had had diabetes since 1909, became pregnant in 1915, and was living and well in 1923; in Case 1207 the patient had had diabetes since 1895 and an eleventh pregnancy occurred twenty-three years later.

In Joslin's Case 812 the diabetes was much more severe, but it first appeared in the course of the pregnancy. This is a rather different story from that of pregnancy occurring in a woman previously diabetic, and as a rule the immediate prognosis is more favorable. Joslin reports eight such cases; we have records of fourteen. Many of these became severe later, but none was severe until some time after delivery of the child.

With the introduction of insulin the treatment of diabetes improved so much that the prognosis of pregnancy in diabetes should now be improved. This is to be hoped for, especially because the incidence of pregnancy in diabetic women is likely to increase. Amenorrhea is an infrequent occurrence in patients receiving adequate treatment early, and vulvitis and cervicitis are seldom if ever found if glycosuria is controlled.

The literature already contains a number of reports of pregnant women treated with insulin. Several of these reports are far from reassuring; others are encouraging. In a case described by Fitz, a young woman after two years of amenorrhea had a return of menstruation and conceived. Abortion occurred at two months, attributed to a fall. In Wiener's case the patient conceived after having had diabetes two years and nine months. The diabetic condition was controlled by diet until four months before term; insulin was then required and during labor "large doses" were necessary. The child was born dead and the mother has not regained the tolerance she enjoyed before pregnancy. Ambard and associates treated a woman, aged thirty-five, with grave diabetes, who gave birth at eight months to an infant with diabetes. The mother died in a few hours, the child after

twenty-three hours. Necropsy revealed lesions in the pancreas of the mother and of the child. The fatal outcome, after hyperglycemia was controlled with insulin, was ascribed to irreparable damage produced in the liver and kidneys by the transient acidosis. Raveno's patient, aged forty-two, had diabetes for two years without treatment, during which time there had been four or five miscarriages. A final pregnancy had gone eight months. The woman was brought to the hospital in coma with blood sugar of 0.444 per cent. Labor was induced; the child died in sixteen hours, the mother surviving.

Gray and Feemster describe the case of a woman, aged forty-four, who had been treated for diabetes for fifteen years, who had had five children and a therapeutic abortion, and who was delivered at term of a living child. On the third day postpartum the mother died and on the fourth day the child died, with symptoms of hypoglycemia. Necropsy failed to reveal a satisfactory reason for the mother's death. In the case of the child the appearance of the pancreas, which contained hypertrophic insular tissue, supported the supposition that excessive insulin formation caused a fatal depression of blood sugar. It is proposed by the authors that this insular hypertrophy occurred in response to the demand of the maternal tissues for insulin.

The encouraging reports are those of Labbé and Couvelaire, Soler and Peters. Labbé and Couvelaire describe a case in which gestation came to full term, ending in the birth of a normal child. Fifty units of insulin were used daily. Soler gave 20 to 40 units of insulin daily to a diabetic woman with acidosis at the seventh month of pregnancy. The general health improved, a badly decompensated heart was restored, and the pregnancy progressed to a normal delivery. In Peter's case of a woman with moderately severe diabetes, labor was induced at the eighth month because of contracted pelvis. The mother made a good convalescence and nursed the baby for nine months.

The two cases which we have to report are significant because diabetes in both was so severe that a favorable outcome without insulin could hardly have been expected. The patients were both young "thin" women in whom diabetes had appeared

abruptly and developed rapidly. Both women had come to us originally with impending coma early in the course of the diabetes, and both were largely dependent on insulin when later they became pregnant. Both had normal pregnancies and delivered healthy children.

REPORT OF CASES

Case 1.—This woman, aged thirty, first came under our observation in November, 1922. She was 5 feet 6 inches tall and weighed 133 pounds; she was intelligent and educated, but very irresponsible. Polydipsia, polyphagia, and polyuria had occurred suddenly the summer before. One brother, two sisters, and one aunt had all died from diabetes.

In the hospital glycosuria was ultimately controlled without insulin on a diet consisting of 50 gm. carbohydrate, 40 gm. protein, and 178 gm. fat. In April, 1923 the patient returned to the hospital in a condition of acidosis, having failed to adhere to the diet. The blood sugar was 0.273 per cent. Tolerance had decreased so that 20 units of insulin were required to prevent hyperglycemia and glycosuria, with the previous diet.

The patient married, against advice, and became pregnant. She did not realize that she was pregnant until she was examined at the fifth month. There were no signs or symptoms of pregnancy except amenorrhea, and since menstruation had been irregular from the time of the onset of diabetes, this was thought not to be significant. During pregnancy she found sugar in the urine whenever she tested for it, but says that she had no symptoms of diabetes, except that she became much thinner. She neglected to follow the diet prescribed for her and ate as she desired, mostly of fruits and vegetables. She took insulin in one dose daily, after breakfast, usually from 20 to 30 units. She felt well and continued to attend to all of her household duties.

At the seventh month a premature female infant was born weighing 3¾ pounds. The confinement took place in a hospital in another city July 3, 1925. After the delivery the patient was placed on the diet which had been prescribed at a previous visit here. This contained 60 gm. carbohydrate, 50 gm. protein, and 220 gm. fat; also 15 units of insulin were given twice daily. On the second day there was a severe insulin reaction so that the dose was reduced to 10 units twice a day. Lactation began on the third day with a copious supply of milk. It was decided that the mother ought not to nurse the baby, so the breasts were allowed to become dry.

The patient consulted us again in July, 1926. She had not kept to a regular diet, but managed her case with little regard for the admonitions of her physicians. She kept her weight at about 135 pounds. She ate chiefly of fruits and vegetables, but also meat, bread, and even a bite of cake on occasions. The insulin dosage was varied daily, depending on what she ate. She said that she found sugar whenever she tested the urine, but she had no other symptoms of diabetes. Menstruation had recurred, but was irregular and the flow scanty. The baby was twelve months old and weighed 15 pounds.

It had been kept in an incubator for the first forty-eight days and had been fairly well since. The mother had tested the baby's urine occasionally, and had at no time observed any evidence of sugar.

Case 2.—This patient, aged thirty-four, was 5 feet 6 inches in height. She entered the hospital May 16, 1926, eight and one-half months' pregnant. Two previous pregnancies had occurred before the onset of diabetes; the youngest child was five years. At the last pregnancy nephritis with marked edema had been a complication.

The patient had had diabetes for two years and two months. The onset was acute, with pronounced polyphagia, polydipsia, and polyuria, and a few weeks later, April 25, 1924, she was brought to us in acidosis. The blood sugar at that time was 0.323 per cent, the plasma carbon dioxid capacity was 19 per cent by volume, and the blood urea 0.041 per cent. The urine contained large amounts of sugar and diacetic acid. One hundred fifty units of insulin were given on the first day to control acidosis. After three weeks in the hospital the patient was allowed to go home on a diet consisting of 50 gm. carbohydrate, 40 gm. protein, 160 gm. fat, glucose equivalent 90 gm., and 1,857 calories. Forty units of insulin were required to maintain the urine sugar free and the blood sugar within normal limits. On this regimen, which was followed very faithfully, the patient gained from 112 pounds to her normal weight of 135 pounds, and was also able to continue with her usual activities.

The pregnancy began in August, 1925. The same carefully weighed diet was adhered to, but during the first four months the dosage of insulin had to be gradually increased in order to keep the urine free from sugar. In the third and fourth months 60 units were taken daily. At the sixth month a dose of 40 units was sufficient. At the eighth month there were symptoms of hypoglycemia on 35 units. During the pregnancy there was a gain in weight from 135 to 154 pounds (slight edema) and a sense of well-being the like of which had not been experienced since the onset of diabetes.

On the admission of the patient to the hospital the urine showed only faint traces of sugar and the fasting blood sugar was 0.078 per cent. Insulin was therefore discontinued. Further observations which had been planned could not be made, since labor had started. Ethylene anesthesia was induced and delivery of the normal 8.5 pound female infant occurred without incident. The placenta was normal both grossly and microscopically. The mother's blood sugar immediately after the delivery was 0.065 per cent, and that of the cord blood 0.071 per cent; the plasma carbon dioxid capacity was 37 per cent by volume. As there was slightly more hemorrhage than normal 500 c.c. of 10 per cent glucose was given intravenously with 20 units of insulin.

The course of diabetes during the puerperium is shown in Table 1, p. 684. On the same diet which had been taken for two years no insulin was required for the first five days, the urine being sugar free and the blood sugar at the upper limits of normal. The breasts filled with milk on the second day, but there was never enough to nourish the baby. The amount diminished even though the breasts were stimulated by the use of the pump and the carbodrate in the diet was increased. An analysis of the breast milk showed that

Table 1

Pregnancy and diabetes

Metabolism before, during and after pregnancy (Case 2)

Date	Diet					Insulin given in twenty-four hours, units	Sugar in urine in twenty-four hour specimen, gm.	Sugar in blood, per cent	Weight, pounds	Breast milk in twenty-four hours, c.c.	Remarks
	Carbohydrate, gm.	Protein, gm.	Fat, gm.	Calories	Glucose equivalent, gm.						
1924											
April 26	20	43	134	1504		150	25.9	0.323	112		Admitted in acidosis
May 23	50	40	160	1800	90	40	0	0.122	114		
1925											
August	50	40	160	1800	90	40		0.100	135		Pregnant
November	50	40	160	1800	90	60	Trace				Third month of pregnancy
1926											
May 15	50	40	160	1800	90	35	0		155		Reaction to insulin
May 16	50	40	160	1800	90	20	0	0.078			Reaction to insulin
May 17	50	40	160	1800	90	0			153		Labor began. Nauseated; [illegible] vomited
May 18	50	gm. glucose given intravenously				20	0	0.065			Delivery of 8-pound girl
May 19	73	35	74	1131	100	0	0	0.153		109	
May 20	73	35	74	1131	100	0	0	0.141		92	
May 21	50	40	160	1800	90	0	0	0.120		92	
May 22	50	40	160	1800	90	0	Trace	0.163		100	
May 23	50	40	160	1800	90	0	Trace	0.145		103	Breast milk contained no reducing sugar
May 24	50	40	160	1800	90	0	Trace	0.173		58	Breast pump used
May 25	98	43	167	2130	140	0	20.7	0.198		38	Breast pump used
May 26	98	43	167	2130	140	0	54.0	0.217		30	Breast pump used
May 27	98	43	167	2130	140	20	23.0	0.265		Weaned	
May 28	98	43	167	2130	140	30	Trace				
May 29	98	43	167	2130	140	35	0	0.185			
May 30	98	43	167	2130	140	25	0				
May 31	98	43	167	2130	140	25	Trace	0.182	122		
June 1	98	43	167	2130	140	25	0				
June 2	68	62	163	2131	120	25	0				
June 3	68	62	163	2131	120	25	0	0.152			Slight reaction to insulin
June 4	68	62	163	2131	120	20	0				
June 5	68	62	163	2131	120	20	0				
June 6	68	62	163	2131	120	20	0	0.130	119		Left hospital
August 22	40	35	100	1200	70	45	0	0.300	129		Sugar appeared in urine with recurrence of menstruation two months after child birth
August 23	75	50	145	1837	120	60					
September 6	75	50	145	1837	120	45					Insulin reduced because of reactions.

it contained no yeast-fermenting sugar. However, with the cessation of lactation the blood sugar increased and sugar appeared in the urine so that insulin was necessary. The patient regained her strength and left the hospital requiring less insulin than formerly, for a diet now higher in carbohydrate, 68 gm. carbohydrate, 62 gm. protein, 163 gm. fat; and 2,131 calories. The weight in the interval had fallen to 119 pounds.

The baby seemed normal in every way. Faint traces of sugar were noticed twice in the urine (Table 2), but the urine of other presumably normal babies in the nursery also showed traces of sugar at times. The blood sugar concentration in blood drawn at different times during the day was about what may be expected in a normal infant (Table 3).

Table 2

Normal child (diabetic mother, Case 2)

Metabolism during first days of life

Date, 1926	Weight, gm.	Food intake		Sugar in blood, per cent	Sugar in urine, single specimen	Remarks
			Amount, gm.			
May 18				0.067		Birth at 12:10 a.m. Cord blood
	3840	Colostrum and breast milk		0.110		Blood eight hours after birth
May 19	3744	Breast milk	198	0.118	0	Breast milk from normal woman
May 20	3686	Breast milk	277	0.120	Trace	
May 21	3614	Breast milk	327	0.141		
May 22	3590	Breast milk	318	0.143	Trace	Blood taken one hour after feeding
May 23	3578	Breast milk	284			
May 24	3666	Breast milk	468	0.050		
May 25	3654	Breast milk	327	0.103	0	
May 26		Breast milk	464	0.131	0	
May 27	3690	Formula	454		0	Formula: one-half whole cow's milk
May 28	3724	Formula	460			One-half water, 10 per cent Karo corn syrup
May 29	3725	Formula	435			
May 30	3744	Formula	420			
May 31		Formula	450			
June 1	3808	Formula	515		0	
June 2	3816	Formula	515			
June 3	3770	Formula				
June 4	3798	Formula		0.107	0	
June 5	3820	Formula				Left hospital
August 22	7325	Formula		0.086	0	Returned for observation when fourteen weeks of age.

Table 3

Normal child (diabetic mother, Case 2)

Blood sugar over one entire day

Date, 1926	Time	Sugar in blood, per cent	Sugar in urine	Remarks
June 4	6:00 a.m.			Feeding
	8:00 a.m.	0.107		
	9:00 a.m.			Feeding
	11:00 a.m.		Negative	
	12:00 a.m.			Feeding
	2:00 p.m.	0.080		
	2:30 p.m.	0.076		
	3:00 p.m.			Feeding
	3:30 p.m.	0.151		
	3:45 p.m.		Negative	
	4:00 p.m.	0.164		
	4:15 p.m.		Negative	
	5:00 p.m.	0.078		
	6:00 p.m.			Feeding
	10:00 p.m.			Feeding

A feeding consisted of 90 c.c. modified milk; formula, one-half whole cow's milk, one-half water, 10 per cent Karo corn syrup. Each feeding contained 7.9 gm. reducing substances calculated as glucose.

Observations and examinations made August 22, 1926, when the baby was fourteen weeks old, showed the child to be growing normally and weighing 12 pounds. There were no evidences of diabetes. The fasting blood sugar was 0.086 per cent and the urine was sugar free. The mother had gained in weight from 119 to 129 pounds, and had been strong enough to take care of the baby herself. With the recurrence of menstruation when the child was two months old, there was a change in the tolerance, the urine containing large amounts of sugar. The insulin dose was increased to 45 units daily, and the diet decreased to 40 gm. carbohydrate, 35 gm. protein, and 100 gm. fat. The fasting blood sugar on August 22, 1926 was 0.300 per cent and the insulin dosage was raised to 50 units. A few days later insulin reactions developed and the dosage had to be lowered again.

DISCUSSION

Pregnancy resulted very fortunately in these two cases. The patient in Case 1 passed through a normal parturition in spite of carelessness with diet and insulin, and so far as can be determined was no worse for the ordeal. The patient in Case 2 had a normal pregnancy, and there is no suggestion that the diabetes is more severe in her case than it was before the pregnancy. There was remarkable improvement in tolerance in the later months of pregnancy; this temporary improvement should possibly be ascribed to insulin derived from the pancreas of the fetus.

A clinical experiment of Carlson and his pupils may be recalled in this connection. When pregnant dogs near term were deprived of the pancreas they did not develop glycosuria so long as the fetal tissues remained alive and the placental connections intact, whereas, as soon as the pups were born, the mother became diabetic. The passage of the internal secretion of the pancreas of the fetus into the blood of the mother is likewise suggested by the hyperplasia of the insular tissue and the hypoglycemia of the child observed by Gray and Feemster.

The cord blood of the child in Case 2 was low and it was again low before a feeding on the eighth day, but no clinical signs of hypoglycemia appeared. In Case 1 severe insulin reaction is said to have occurred on the second day after delivery, and in Case 2 the blood sugar at the time of delivery was very low. Also in Case 2 the urine continued to be sugar free and the blood

sugar relatively low for five days after the child's birth, whereas no insulin was given during this period. Fetal insulin can hardly explain this remarkable tolerance. The phenomenon is exactly the same as that observed by Macleod in a depancreatized, insulin-treated, pregnant dog. This animal nearly died in hypoglycemic convulsions after delivering, and Macleod maintains that the reason for such a reaction is the passing of sugar from the blood to the breasts as these fill with milk.

In view of these considerations it seems to be very important to guard against hypoglycemia not only during the delivery of diabetic women, but also in the after-care of mother and child. The analysis of the blood of the babe in Case 2 was on capillary blood from the toe by the Hagedorn and Jensen procedure. This method avoids the necessity of venipuncture and permits much more frequent estimations than would be possible otherwise. The experience of Gray and Feemster prompted us to start feeding the child in Case 2 as soon as it was born. Instead of delaying as is customary until the child's mother could provide for it, we gave breast milk from another mother within three hours after the delivery and continued six feedings a day thereafter (Table 2). Treatment of the mother in Case 2 followed closely the usual practice with diabetic patients undergoing surgical operation.

SUMMARY

The successful completion of pregnancy in two young diabetic women treated with insulin is reported. Diabetes was moderately severe in both. They had been under treatment previously for severe acidosis and depended largely on insulin when they later became pregnant. In one case the tolerance after being aggravated during the early months of pregnancy underwent decided progressive improvement as term was approached, suggesting that the growing fetus was supplying the maternal tissues with insulin. In both cases hypoglycemia developed at delivery or shortly after at the time the breasts were filling with milk.

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SOME ASPECTS OF TUBAL INFLATION

LAWRENCE M. RANDALL

In the last Mayo Clinic Volume of Medical Clinics of North America the technic of tubal inflation in making diagnoses of sterility in the female was discussed. I now wish to present further considerations of this test which are important. Experience in the Clinic shows that inflation has opened a closed tube in less than 1 per cent of cases. When one considers the usual infectious etiology of tubal occlusion and the resulting lesion, it is remarkable that an opening is ever effected. Instances in which pregnancy has followed inflation are known to all, and credit for it has been given to this useful piece of diagnostic machinery, but it seems more logical to assume that actual occlusion due to a lesion has not existed in many of these cases and that some other factor was responsible for the sterility.

Thorough cleansing of the cervix which is necessary in order properly to perform tubal inflation must often temporarily remove a common barrier to conception, that is, a highly tenacious and often infected cervical plug. We have had two instances of an unlooked for therapeutic result following tubal inflation, relief from a severe obstructive type of dysmenorrhea lasting for several months. In one instance, painful menstruation, severe enough to require opiates, was the patient's sole reason for visiting the Clinic. She had not borne children. Investigation of the husband revealed azoöspermia. The inflation was repeated five or six times at one sitting. It showed occlusion of the tubes to 200 mm. of mercury and the patient was sent home. She has been free from pain for several months. The position of the uterus and the cervical stenosis could not have caused her trouble. She had not taken medicine to inhibit or relieve pain.

The selection of the proper time to perform inflation in relation to the menses is of some importance. It is entirely conceivable that premenstrual congestion can affect the level at which the gas will pass through the tube into the peritoneal cavity. A diagnosis of tubal stenosis and even occlusion is thus possible in a perfectly normal case. A recent experience of my own shows that it is possible to force endometrium out through the tubes if inflation is done too near the menstrual period. A patient presented herself for investigation of sterility. Examination revealed a markedly retroverted uterus which was causing symptoms which seemed sufficient to explain the sterility. It was obviously necessary to know the condition of the tube before advising operation for the cure of the sterility. Inflation done about four days after the menstrual period determined normal patency. The patient returned home for the operation. A few months later her surgeon informed us that at operation he had found a pea-sized mass of endometrium on the peritoneum immediately below the abdominal ostium of both tubes. It is reasonable to suppose that this tissue was forced out at inflation. The position of the uterus probably had something to do with this; it would not be likely to occur in an anteverted organ. In any event, inflation is probably best carried out midway between menstrual periods; the accuracy of the test is then greatest, and the chance of repeating this experience obviated.

Spasm of the uterine muscle probably has considerable bearing on the result of tubal inflation. The muscle in the uterine cornu around the intestinal end of the tube is believed to have sphincteric action. If this functions during inflation, the result is stenosis or occlusion. Improper performance of inflation may be misleading, since by rapidly increasing the intra-uterine pressure the gas cannot escape through the tube as fast as it enters through the cervix. This excess of pressure may be responsible for a spasm of the uterine muscle. We find that three bubbles a minute passing through the water trap raises the pressure slowly enough to obviate this. There remain, however, a few instances in which the test is correctly performed and the spasm factor is present. To exclude these tincture of bella-

donna is used to relax the muscle. A dose of 30 drops is given the evening before and repeated in the morning, and again at 11 a.m., just before the test is made. If nonpatency is again the result, we must conclude that a pathologic condition in the tube is the cause.

We have come to depend on the behavior of the pressure registered in the mercury manometer during the inflation and the reaction of the patient following the test to make a diagnosis of the condition of the tube. As an aid to this we recently took roentgenograms of the dome of the diaphragm with the patient in the upright position, and of the right dome and parietes with the patient in the left lateral position immediately after inflation. Not more than 200 c.c. of carbon dioxid were allowed to pass through the tubes in each case. This amount was found sufficient to cast a shadow on the plate, but in no instance was it enough to cause more than temporary discomfort because of the shoulder pain. Roentgenograms were discontinued after the first 100, as they afforded no added information for the individual case. If patency existed, shoulder pain resulted and the roentgen-ray showed the bubbles of gas. In the nonpatent tubes shoulder pain was absent and no bubble was seen, so that the plate was unnecessary.

The diagnosis of tubal occlusion if a woman is sterile does not end the consideration of the case. Many women desire to know the possibilities of surgery in their case. Tubal inflation may only reveal that the tube is closed, and only a guess can be made as to the site of closure from the patient's reaction during inflation. Discomfort in either or both lower quadrant is often observed when occlusion is at the fimbriated extremity, and the sensation is confined to the uterus and hence to the median line if the tubes are sealed at the uterine portion. This information is unreliable. During the last six months we have used lipiodal (as reported elsewhere) to assist us in the further consideration of sterility in women with occluded tubes. The roentgenogram affords valuable information in deciding for or against operation.

FOUR CASES OF URINARY CALCULI FROM WHICH PROTEUS AMMONIÆ WAS ISOLATED*

BENJAMIN H. HAGER AND THOMAS B. MAGATH

Case 1.—A boy, aged fifteen, complained chiefly of pain and difficulty in urination. His history was irrelevant except for two operations. The appendix had been removed three years before examination at the Clinic because of pain in the right hip which had troubled the patient for two weeks and was so severe that he could not walk. The symptoms disappeared. Two years later an enchondroma in the region of the right groin was removed, and lavage of the bladder was carried out for one week. The patient said there had been swelling and a limp for about three or four months before operation. One to two months after operation he began to have burning on urination, noted a small lump on the lower side of the penis, and began to have some pain. In July, 1925 he began to pass what looked like pus and was troubled by frequency (six to seven times daily) and nocturia. The symptoms were progressive, but he did not mention them until January, 1926, when they had become so severe that he could no longer hide them. He had been in bed ever since.

On physical examination he weighed 99 pounds; his systolic blood pressure was 120 and diastolic 102; his tonsils were enlarged 3; there was a purulent and bloody urethral discharge, and marked tenderness over the penal urethra, the posterior half of which was nodular and indurated. Urinalysis revealed a specific gravity of 1.015 alkalinity, red blood cells 2, an occasional pus cell, phenolsulphonephthalein return of 50 per cent, and blood urea 22 mg. Examination of the blood showed that the hemoglobin was 72 per cent and that there were 4,240,000 erythrocytes and 9,200 leukocytes. A roentgenogram of the kidney, ureter, and bladder revealed only a large stone in the bladder (Fig. 91).

A diagnosis of vesical lithiasis was made and suprapubic cystostomy was performed. A stone, measuring 2.5 by 2 cm., was removed (Figs. 92 and 93). A very foul cystitis made it seem advisable to maintain suprapubic drainage for some time. A qualitative analysis of the stone showed that it was composed of phosphates and carbonates.

A culture of the urine from the bladder, as well as that passed by the urethra, showed *Proteus ammoniæ*. The disease was then recognized as an infection with *Proteus ammoniæ* and treatment instituted to rid the bladder and urethra of it.

* Read before the New York Academy of Medicine, New York City, May 21, 1926.

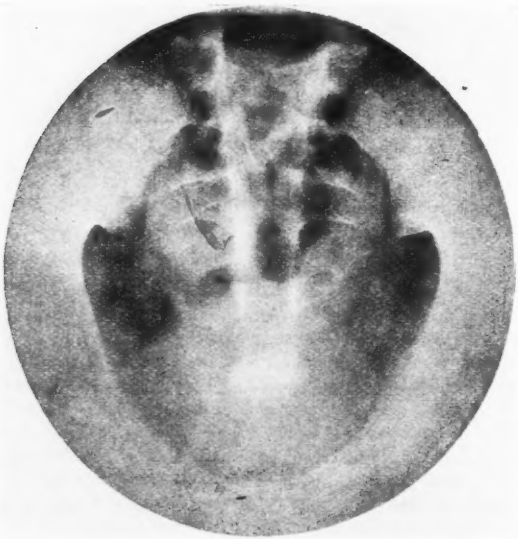

Fig. 91.—Shadow of stone in the bladder.

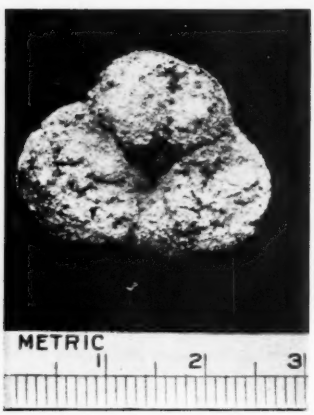

Fig. 92.—Photograph of the stone in the same case as in Fig. 91.

Fig. 93.—Another view of the same stone as shown in Figs. 92 and 93.

Following the suprapubic cystostomy practically all the urine drained through the stoma, very little passing through the urethra because of marked burning and pain. The incrustations in the posterior portion of the urethra remained fixed in spite of the daily irrigations of bladder and urethra.

Some time later, under general anesthesia, urethrostomy was performed at the angle of the penis and scrotum, and by means of a gallbladder scoop four large pieces of incrusted material were removed from the posterior urethra. The incrustations anterior to the point of incision were also removed by curetment. A sound was then passed through to the bladder without difficulty. The incision was closed, and a soft rubber catheter inserted through the urethra into the bladder. Following this the patient made a very satisfactory recovery with no recurrence of symptoms during the remainder of his stay.

Case 2.—A woman, aged sixty-six, complained chiefly of frequency and hematuria of five years' duration. Fifteen years before a vaginal suspension of the uterus had been performed. At the onset of the trouble there had been

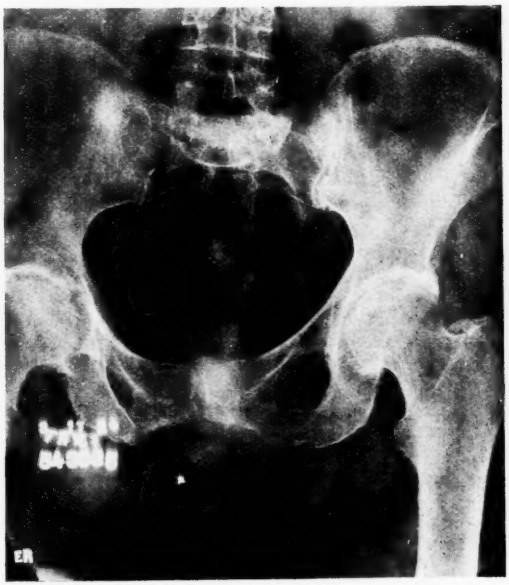

Fig. 94.—Oblong shadow over left symphysis pubis.

some daily and nightly frequency. This gradually became worse until during the last three months she voided twenty times a day and twenty times a night, and felt pain over the bladder, particularly at night when lying

down. The pain gradually subsided, but returned again in the morning when the patient arose. During the last three months hematuria had been constant. There were no renal pains.

On physical examination the systolic blood pressure was 240 and the diastolic 115; the heart was enlarged to the left and had a systolic murmur; there was slight edema of the ankles. Analysis of the urine showed that the specific gravity was 1.021; that the urine was alkaline and contained albumin 4, red blood cells 4, and pus 1. A roentgenogram was made of the kidney, ureter, and bladder, and a shadow, 3 by 2 cm., was observed over the symphysis pubis (Fig. 94). Cystoscopic examination disclosed a diverticulum 1 by 1.5 cm., opening in the right base, and a stone 2 by 2 cm., but neither ureteral meatus could be seen.

The stone was removed by crushing. At the time a cystoscopic examination showed that the bladder was much ulcerated, the mucosa was necrotic, and the bladder was contracted to a capacity of from 30 to 60 c.c., with an irregular outline. The possibility of neoplasm was not excluded. *Proteus ammoniæ* was cultured from stone fragments. The patient felt so well after the crushing of the stone that she had no further treatments.

Case 3.—A woman, aged forty-four, came to the Clinic because of burning, frequency, dysuria, slight hematuria, and nocturia (three or four times). She had begun to pass small stones from the urethra. Twenty years before perineorrhaphy had been performed, repair of the rectovaginal fistula twelve years before, and perineorrhaphy again three months before.

The last time the perineum was repaired the cervix was amputated and the uterus suspended to the bladder. The perineal stitches held, but five days after operation a rectovaginal fistula developed. Feces and gas passed through the vagina when the bed-pan was used, although not when the bowels moved in a sitting position. Cystitis, burning and frequency with dysuria and slight hematuria, and nocturia (three or four times) developed two weeks after operation. The patient now began to pass small stones from the urethra. Cystoscopic examination prior to admission revealed an area of incrustation and papilloma of the bladder. The latter was cauterized, and at that time a stone was seen in the bladder. The patient now complained of constant pain in the pelvis, which was much worse during and after urination.

On physical examination the patient appeared well nourished; there had been a moderate amount of dental repair; the abdomen was tender; there were no masses over the bladder area; the pelvic perineum was somewhat lacerated; the cervix had been amputated; no lateral masses were found, and the rectal sphincter was scarred. The urine had a specific gravity of 1.010; it was alkaline and microscopically normal. The hemoglobin was 79 per cent; the erythrocyte count was 5,360,000 and the leukocyte count 11,000. The tonsils showed slight fibrous infection with fluid pus. The Wassermann test was negative. The blood urea was 18 mg. for each 100 c.c. Roentgenograms revealed a large calcified area in the region of the bladder (Fig. 95). The *p*H of the urine was 8.2. Cystoscopic examination showed that the capacity of the bladder was from 120 to 150 c.c., that there was diffuse inflammation and a large calcareous deposit, 5 by 6 cm., resembling a stone. Neither meatus could be seen.

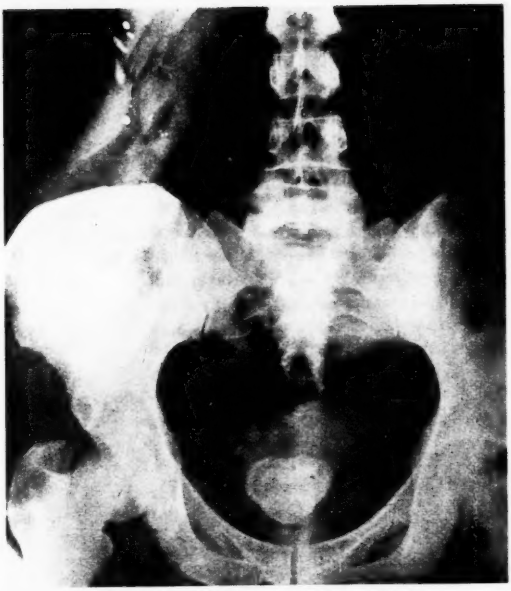

Fig. 95.—Large shadows in region of bladder.

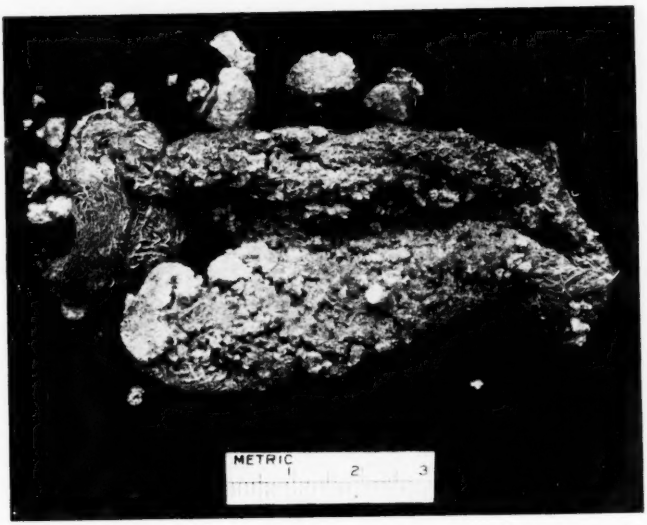

Fig. 96.—Photograph of gauze and incrustations removed simultaneously.

The next day litholapaxy was performed and the calcareous deposit which had been thought to be a stone proved to be a sponge heavily incrusted with stony material. This was removed through the urethra with the lithotrite. The sponge was of the usual size, 7.5 by 10 cm., and covered with an adherent phosphatic deposit (Fig. 96). The urethra was somewhat torn, and bled freely following removal of the foreign body. Cultures made from the calcareous masses showed *Proteus ammoniæ*.

Eight days after operation the cystoscope showed that there were few remaining areas of cystitis. The urethra was still somewhat, dilated, but the mucosa was almost normal. The dilatation of the external urethra was apparently reduced. The patient was in excellent condition, with good sphincter control, and she was sent home.

Case 4.—A man, aged sixty-six, gave as his chief complaint frequency and burning of three or four months' duration. He had been crippled when an infant. He had had typhoid fever, diphtheria, pneumonia, and influenza

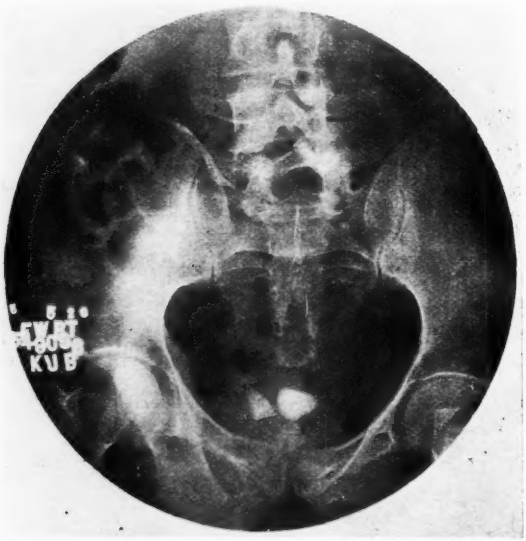

Fig. 97.—Multiple laminated shadows over the area of the bladder.

in 1924, and malaria on different occasions. A two-stage prostatectomy had been performed in October, 1925. About six weeks later the patient began to have frequency, voiding perhaps every fifteen minutes, but never passed more than from 60 to 120 c.c. of urine at a time. It was accompanied by some burning. Nocturia was progressive until at the time of examination,

when the patient got up four or five times a night, passing a total of scarcely more than 250 c.c. The urine then had a very strong odor.

On general examination the patient appeared senile and emaciated; the left leg was atrophied. Much pyorrhea and numerous root tags were noted. The chest was tympanitic; pulsus alternans was noted, but no cardiac enlargement; there was considerable arteriosclerosis of the peripheral vessels. The prostate showed multiple hard indurated areas in the prostatic capsule, particularly on the left side. Urinalysis revealed alkalinity; the urine contained pus 1, cells 15, and had a combined function of 50. A roentgenogram showed multiple laminated shadows over the area of the bladder (Fig. 97). *Proteus ammoniæ* was isolated in pure culture from the urine.

Under sacral anesthesia a cystoscopic examination and litholapaxy were performed. There was some residual prostatic tissue in the neck of the bladder, together with diffuse inflammation and multiple large cellules in both bases and posterior wall. Two of the stones were found in pockets in the prostatic capsule. These were pushed back into the bladder and crushed. Following litholapaxy fragments were removed, but there were multiple areas of firm incrustations in the prostatic capsule and base. An examination of the calcareous material showed it to be made up of phosphates and carbonates.

Various factors and numerous conditions have been regarded as the cause of stone formation. That no single mechanism suffices to explain the modus operandi of all calculus formation is apparent. The actual cause appears so intimately concerned with the predisposing factors that an effort to separate one from the other becomes very difficult. Neither is it possible to distinguish between the actual cause of lithiasis and those factors which might be regarded as secondary.

In a previous presentation on the etiology of incrusted cystitis with alkaline urine we reported the observation of free floating stones in the bladder and explained their occurrence as a result of the activity of a certain bacterium.[3] Since then we have extended our observations to a case of calcareous pyelonephritis which could be attributed to this bacterium.[2] Recently we have observed these four cases of vesical calculus, from which this organism has been isolated, that seem worthy of a report.

Since the genus Salmonella is not clearly worked out as yet and contains many species that do not suggest close resemblance to each other, it was thought that this new organism could be placed there for the time being, pending a further study when more strains would be available. We have now been able to

study twenty strains and, as a result, believe that the organism does not belong in the genus Salmonella because the majority of the strains liquefy gelatin, grow with ameboid colonies, and all appear to be protein destroyers. They have the characteristics of the genus Proteus, except that they do not ferment sucrose. Since the fermentation of sucrose appears in the generic description of Proteus, we propose to modify the genus to include some forms that do not ferment sucrose. As this seems to be the most logical disposition of the species the name becomes *Proteus ammoniæ*.

The literature contains many accounts of the finding of Proteus in the urine, and authors have in the past ascribed the formation of "volatile" alkaline urine to its presence. Since the detailed studies of such forms are not available, we must conclude that the form was identified by its ability to liquefy gelatin, the spreading of colonies, the putrid odor, and, if sugar studies were made, by its ability to ferment sucrose and its failure to ferment lactose. Judging from our own experience and, indeed, the statements of most authors, *Proteus vulgaris* must be the species that is usually found.

Whether the particular organism has been isolated before in the study of incrusted cystitis cannot be told from the literature, but it has been noted by some authors that various bacteria, notably "Proteus, Staphylococcus, colon, the tubercle bacilli, and the Micrococcus urea," have been associated with the disease.[1] It is quite possible that the Proteus referred to may have been *Proteus ammoniæ*, but if it was so identified it was because its inability to ferment sucrose was overlooked or not taken into consideration. We are unable to find a description of a species of Proteus that corresponds to the specific description of this bacterium. In this connection we wish to call attention to the obvious fact that finding an organism in the urine does not per se constitute evidence that it has caused a lesion which now exists in the urogenital tract. Proof depends on fulfilment of Koch's postulates or their equivalent.

The rôle played by organisms in changing the acidity of the urine in man has formed the basis of much study in the past.

Many organisms have been said to be able to make the urine alkaline. One of the most significant of these is "*Bacillus proteus urinæ*," described by Horton-Smith in 1897. He isolated this organism in a case of acute cystitis which developed following catheterization. The description of the symptoms and findings strongly suggest that the patient suffered from incrusted cystitis, but as there was no ocular examination of the bladder this can remain only a guess. The organism described had the power of reducing urea to ammonia in sterilized urine, which we now know to be a common property of the genus. As the sugar-fermentation tests are not recorded it is impossible to tell whether or not he was dealing with the organism we describe.

Other members of the genus Proteus have been found in cases of chronic cystitis and the alkalinity of the urine has been properly ascribed to their presence. Shohl in 1920 showed that *Bacillus coli* would eventually produce an alkaline reaction in urine, but the process takes about five days in the test-tube, so that, unless retention was very marked, *Bacillus coli* could hardly be considered a factor in the production of alkalinity, especially in the case of incrusted cystitis in which the urine may be voided as often as every fifteen minutes.

We believe that, in the majority of cases of alkaline cystitis, barring those in which the alkalinity of the urine is due to metabolic changes and the secretion of alkaline glandular fluids, some member of the genus Proteus is present in the bladder. But, as a matter of fact, alkaline urine, that is, urine with a *p*H above 7, is not common even in various types of cystitis, if the urine is tested immediately after it is voided. One must remember that litmus paper often turns below 7, and that to use this as a criterion is not correct.

From our experimental work and a study of the cases of incrusted cystitis associated with alkaline urine, it seems to us that the presence of Proteus organisms in the bladder is important. Whether any other member of the genus beside *Proteus ammoniæ* can produce the pathologic picture made by this specific organism is not known. The facts are these: We have isolated this organism in many cases of incrusted cystitis, and in all so clinically

diagnosed since its identification was first made; we have isolated no other organism of this genus in such cases, but have occasionally isolated other members of the Proteus genus (vulgaris) in cases other than incrusted cystitis.

When a lesion is made in the bladder in experimental animals and the organisms are introduced, typical incrusted cystitis develops and, in a certain number of cases, free bladder stones. The method seems obvious. The precipitation of the earthy metals in alkaline mediums causes the formation of these alkaline earthy salts on the lesions. Some of them break off and are built up into stones of large size in the bladder by the same process. If the urine were not alkaline the phosphate-carbonate stones would not form.

It seems evident, therefore, that *Proteus ammoniæ* after invading the bladder can, under favorable conditions, produce true vesical calculi, and the mechanism by which such stones form is probably a continuous precipitation, on already existing lesions, of the alkaline inorganic salts resulting from the alkalinity of the urine produced by *Proteus ammoniæ*.

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HYSTERICAL PARALYSIS

HARRY L. PARKER

To the general public the term "paralysis" has a sinister meaning, and much pity and awe is expressed for the unfortunate person who is doomed to go through life dragging a useless limb. The sudden and dramatic cure of one of these sufferers after possibly years of disability produces a corresponding degree of veneration for the agency bringing about this happy result. The vast array of crutches and canes at the various religious shrines supposedly endowed with miraculous power bespeaks the truth of the text "Thy faith hath made thee whole." In revival meetings when emotional tension becomes high sudden recoveries may take place in those whom grave and learned physicians had prognosticated would never use their limbs again. It is no wonder, therefore, that with a physician confronted by a patient whose paralysis he suspects as being hysterical there is a deep and troublesome fear that his diagnosis may be mistaken. To make a frank diagnosis of hysteria always means that the burden of proof rests on his shoulders, and the only proof is that he has the ability to cure the disease by simple psychogenic means. On the other hand, to pronounce the paralysis incurable and to hear later that the patient has drifted into the hands of a charlatan whose pompous power of suggestion removed the paralysis is enough to cast a slur on the reputation of the physician and the power of his healing art. The burden of responsibility is heavy in dealing with such patients, and a silent tongue is essential until careful, painstaking examination and even prolonged observation make the diagnosis assured. It is the one type of case wherein it is dangerous to jump to conclusions, since first impressions may be totally erroneous and hasty judgment shame us

the rest of our lives. The following case records reveal many of the difficulties and problems in connection with hysterical paralysis and convey some suggestions as to their solution.

REPORT OF CASES

Case 1.—A young woman, aged eighteen, came to the Clinic February 18, 1924, complaining of paralysis of the left arm and of fainting spells. Two years before she had fallen, striking the ground on the left shoulder and left side of the head. Following this there was considerable pain in the shoulder joint with disability. The arm had been tightly bandaged to the side for three weeks. She then still complained of pain in the shoulder, and a diagnosis of dislocation was made. An attempt at reduction was unsuccessful, even though the operator put his foot in the axilla and pulled forcibly on the arm. A week after this she noticed numbness and paralysis spreading upward from the fingers to the wrist, elbow, shoulder, and scapular muscles. She lost all power in her fingers and arm and the whole upper extremity dangled helplessly with a flaring outward of the scapula and the general appearance as if the whole upper extremity was ready to drop off. She became nervous and restless and vision in the left eye failed. She had been told that there was no further hope of recovery and that the nerves of the arm had been torn loose from the spine. The area on the left parietal region of the head, the point of original injury, became tender and painful and she complained of violent headaches in this area. At the height of these headaches she had spells of falling and would lie unconscious for from a few minutes to an hour. On regaining consciousness she would jump up, strike at persons, bite, yell, and career around the room wildly. During these periods the left arm would remain limp and helpless, although the rest of her body was violently active. After some minutes of this excitement she would lie down again, relax, and gradually become normal, complaining, however, of weakness of exhaustion. She would then sleep for an hour and awake feeling perfectly well with no memory of what had transpired. In all there had been fourteen of these attacks.

The left upper extremity was apparently completely paralyzed. The arm was perfectly toneless and could be twisted in all directions. The whole shoulder and scapula sagged downward. This upper extremity, the left side of the face, and neck and thorax down to the seventh intercostal space were also anesthetic to all forms of sensibility. There were, however, no trophic changes in the fingers, no circulatory disturbance, and the muscles were not atrophied. The tendon reflexes were present and active and there was a ready response to stimulation of the muscles by faradic and galvanic current. Although the patient complained of total loss of vision in the left eye, she was persuaded to read with it when the right eye was covered with a thick convex lens. Within three weeks under faradic stimulation and reëducation the patient recovered full use of her upper extremity, regained the sight of her eye, and the anesthesia disappeared. She left us with complete restoration of function in a limb that had been useless for nearly two years.

In the study of the psychic processes of this patient the outstanding feature was her personality. She was cold, unemotional, and showed a marked indifference to her physical disability. Her general attitude was such that it seemed as if for her the limb did not exist. She seemed detached from all her physical troubles and perfectly satisfied to carry on life without her left arm. When she was commanded to use the limb she would look at the examiner with pained surprise and make no attempt whatsoever to do it. This general attitude is characteristic of patients with hysteria, and contrasts sharply with that of patients with paralysis due to organic disease. In their case the whole desire is to accomplish as much as possible, and their attentions and efforts are forcibly directed toward the paralyzed limbs. It is only in extremely severe cases that no movement is accomplished, and then manifest signs of organic disease are present. The hand may be helpless, but some movement may be possible at the elbow joint and fairly good function at the shoulder. On the other hand, in hysteria the loss of power is complete, and with the anesthesia commences from a sharp line either around the shoulder or further up on the trunk, defying all the laws governing the distribution of sensation and power according to the anatomical arrangement of the nervous system. The paralysis here was massive and the arm and shoulder sagged downward with the scapula which was also displaced backward. This is unusual in brachial plexus injuries when the arm hangs loose from the shoulder joint, but the trapezius which is supplied by the eleventh cranial nerve preserves the line of the shoulder as well as allowing the patient to raise the shoulder to the ear. This movement the patient could not make, and were we to assume the presence of an organic lesion, the cranial nerves would have to be implicated as well as the brachial plexus; even more extraordinary from the standpoint of organic disease was the loss of vision in the eye on the same side. The anesthesia also had little regard for the difference between spinal and cranial innervations, and the convulsions were of the hysterical type wherein the patient bites, kicks, and performs well coördinated purposeful movements highly colored with a strong emotional tinge. In the final analysis of

this case it was discovered that when the patient was injured she had been treated by a young, unmarried physician. He had impressed her with the seriousness of her condition as well as producing a considerable effect on her unstable, erotic personality. She was enamored of him, and he did not reciprocate her affections, but her disability represented a bond between them which she did not willingly desire to relinquish. Later on the dictum of others that she had a severe, incurable paralysis justified her assumption of a paralyzed arm.

Case 2.—A young man, aged nineteen, was brought to the Clinic July 27, 1926, because of paralysis of both lower extremities. Three weeks before he had complained of fatigue especially in the lower extremities. This had increased for three days while he was actively engaged in farm labor. On the fourth day at noon he ate a hearty dinner and on arising from the table complained that his limbs were so tired that he needed support to walk. He was helped to his bed with his limbs dragging helplessly behind him. After reaching the bed both lower extremities became completely paralyzed so that he was unable to move any part of them. The family physician was called and he pronounced the disease to be one of inflammation of the spinal cord, and gave a very poor prognosis. The patient had remained paralyzed up to the time he was admitted to the Clinic.

Examination revealed a healthy looking youngster who seemed physically normal in every way except for the outstanding complaint. He was wheeled around in a chair by his aged father on the assumption that he was totally unable to move any part of the lower extremities. However, when he was helped onto a pair of crutches he made remarkable progress with the thighs forcibly adducted, and all the muscles of the pelvis and lower extremities contracted into a rigid pedestal which he moved, using the lower lumbar spine as a hinge. It was obvious on watching his movement that firm contractions of the muscles of the lower limbs and pelvis were necessary and actually these could be seen contracting and relaxing normally. He could arise from a prone to a sitting position without using his hands and the quadriceps muscles could be felt contracting in the process. One lower extremity was raised in the air and he was told to sustain it in this position, but when the supporting hand was withdrawn it dropped helplessly with a loud thud. On the other hand, if his attention was engaged elsewhere and the hand was slipped away quietly, the limb might remain suspended in the air for a few seconds. When he was up on his crutches and these were withdrawn he fell unhesitatingly to the floor regardless of personal injury and remained there. All tendon reflexes were present and active, there were no abnormal reflexes, and the shape, contour, feel, color, and tone of the limbs were normal. There was no anesthesia, sphincter control was normal, and the muscles responded actively to faradic stimulation.

He had, as in the preceding case, the detached, indifferent attitude of an

hysteric person. His limbs seemed no longer a part of him and he allowed his father to tie his shoes, dress him, and wheel him around. On commanding him to use his limbs he simply stated that he could not do so and made no particular effort in that direction. He showed little concern for his helplessness, and while expressing a desire to get well seemed in no hurry to reach that happy state.

He was placed in a hospital and given faradic stimulation with plenty of suggestion and persuasion. Little result was obtained until after the fourth day, when following a period of meditation he was commanded to get up and walk. He suddenly left his bed and walked unaided, at first hesitatingly and like a child, but later, confidence being restored, within an hour he was almost running to the telegraph office to send messages to his father, his sweetheart, and his friends that his paralysis had gone.

The psychic difficulty here was represented by a reaction from an intolerable situation. The patient had been studying hard to become a medical missionary and had made high grades. The paralysis had developed during a summer vacation while he was working on his father's farm, and just prior to its occurrence he had contracted to teach the following year in a very disagreeable locality. This was for the purpose of replenishing his family funds and meant abandonment of his studies for the coming year with menial employment and all sorts of social difficulties. He worried over this and lost sleep and became depressed since there seemed to be no way of avoiding that into which he was being forced. Following the meal, when the family touched on his future in their conversation, release came to him in the form of hysterical paraplegia. All difficulties were now solved and he reached a mental state of peace and self-sufficiency which was shown by the indifferent, apathetic, detached attitude which he exhibited here. In the course of his treatment a solution of these difficulties was reached through the aid of the family, which helped materially in his final recovery.

While the mental mechanism involved in the production of hysterical paralysis is always interesting and important, it is far better in the beginning to attempt to reach a diagnosis by methods of physical examination and observation before delving into the domestic environment and social problems of the patient. Too often we are led astray by the discovery of some particular phase of psychic agony which is convulsing the pa-

tient's inner thoughts, and we may assume erroneously that it is the whole cause of a disease actually due to gross structural alteration of tissue, altogether unassociated with the social or domestic grief he may be experiencing. In this vale of tears we all have enough trouble to make us hysterical if only we were predisposed to it, and few of our patients, whatever their disease may be, are free from some of the insoluble problems of life. It is far better to make the diagnosis first on distinct, positive, and objective signs and later hunt up the psychic mechanism that is at the root of it. The discrepancies and inconsistencies in the rôle displayed by an hysteric person are often striking and command the attention of the observer. In the second case the patient could not move his limbs in bed, yet could contract the muscles of his thighs and guide his feet when walking on crutches. The paralysis that he assumed while sitting or lying was massive and total from the waist down, yet the limbs appeared normal, he had normal sensation, and the sphincters were not affected. In practically every case of hysterical paralysis some discrepancy may be found between the patient's professed power and his actual power. A striking example of this occurs in some cases of hysterical aphonia when the patient can only talk painfully and slowly in a whisper yet can sing with great power and dramatic expression.

Case 3.—A woman, aged forty-four, was brought in an ambulance to the Clinic December 7, 1925, because of a broken back and paralyzed limbs. Three weeks before her admittance she had been down town shopping and while in a departmental store the elevator in which she was riding fell two stories. She remembered the crash, but immediately became unconscious. She was rushed to a hospital, regained consciousness on the way there, and complained bitterly of an occipital headache, vomiting and nausea. She had to be catheterized the same evening and twice the next day. Spinal puncture performed the next day relieved the headache, and a clear fluid slightly under pressure was withdrawn. She was free from pain within a few days and during the whole time in the hospital was perfectly able to move her lower limbs in bed. She left her bed about five days before coming to the Clinic still feeling weak and rather shaky. She found to her surprise on attempting to walk that her limbs crumpled under her and she fell with a crash to the floor. Thereafter at each attempt she made to walk the same thing occurred and her attending physician concluded that she had sustained a broken back with resulting paralysis.

The patient was rather undernourished and nervous. She was found sitting up in bed very comfortably and was very carefully groomed. It seemed to her that she was unable to walk and she demonstrated how perfectly she could move her limbs in bed. She was assisted to the floor by her attendants and was requested to perform to the best of her ability. Even before her limbs reached the floor and while still sitting on the edge of the bed she clutched wildly and with the grip of a drowning man the supporting arms of those around her. She was almost carried on the floor. Even then her arms seemed insufficient to support her weight, and her grip loosened so that she fell in a heap on the floor with an expression of discouragement and chagrin.

Careful neurologic examination showed no changes in her limbs, and the power as tested in bed was normal. There was a fluctuating mild disturbance of sensibility up to the middle of the thighs. There was tenderness over the lower lumbar spines. Roentgenograms taken of this region and of the whole spine showed no changes. I was, therefore, able to exclude any possible fracture of the vertebræ.

A diagnosis of hysterical paraplegia was made and treatment in the form of suggestion, persuasion, and reëducation instituted. Faradic current was also used chiefly while the patient was attempting to stand. She improved rapidly, but at first her gait was feeble and she required two people to support her. Later on one was necessary, and toward the end the walls, the furniture, and a casual passer-by were sufficient. It was some time before she could be persuaded to cross an open space unaided. In the early stages of her reëducation the efforts made to remain upright were wild and exaggerated. She clutched at everything and everybody with great show of emotion and ejaculation of fear, but after three weeks she could walk normally, and finally was dismissed from observation, according to her story, perfectly well.

The term "astasia-abasia" has been coined to cover those cases of hysterical aphasia wherein the patient can use the lower limbs perfectly in the recumbent posture, but can neither stand nor walk. In the case of this last patient there was perfect strength, tone, and coördination in the lower extremities as tested when she was lying in bed, but when put on her feet she promptly fell with every show of emotion. These two features, the discrepancy between function with the patient lying down and that while she is attempting to walk and her exaggerated behavior in the upright position, are extremely diagnostic of this type of hysterical paraplegia. A patient who has organic paralysis will use his power to the utmost to preserve the erect posture, while an hysterical patient will either make no attempt at all and fall like a log, or with great emotional display perform a riot of move-

ments which take much more skill, strength, and balance than the relatively simple acts of standing and walking. To simulate the grotesque, staggering, plunging movements of some of these patients when on their feet may even require the skill of an acrobat. The psychic factors in this patient were not very complicated and as in many hysterical persons they represented a regression to behavior in childhood. She was possessed of a shallow, superficial personality and had lived an uneventful, useless, artificial existence without thought of anything except her own selfish needs. She had had no children, had very little work to do, and was spared the harsh, yet ennobling struggles of life. She had neither any striking vices nor redeeming virtues. The crash in the elevator therefore was a very terrifying thing to her and knocked the well-ordered, complacement scheme of things which had been arranged for her into bits. She had believed she was maimed and paralyzed for life, and in this thought she was materially assisted by the opinion of those who attended her. It took just so much effort as we put forth to get her back on her feet again and restore her confidence in the wholeness of her body and the fitness of things. No doubt for the rest of her life this experience would seem to her to be of surpassing magnitude.

DIAGNOSIS

The methods of diagnosis in the cases of hysterical paralysis have been suggested in the cases outlined here. The first necessity is a careful and detailed neurologic examination to exclude organic disease. In many instances it is better to assume its presence until proved otherwise. The second is the determination of the inconsistencies and discrepancies in the state of paralysis that the patient assumes and a comparison of it with the known postures and disturbed functions of paralysis due to organic disease. The third point in the diagnosis is a careful assessment of the patient's personality with his or her reactions to the disease and general behavior during the course of examination. The fourth is a survey of the situation under which the paralysis appears and the associated events occurring in the patient's life history with the psychic reactions thereto. The problem of

traumatic hysteria with medicolegal features comes under this heading. In a case wherein a patient is injured in the course of his employment and paralysis follows, a very careful history is required covering every minute detail of the alleged injury and the course of development of the paralysis. The relation between the patient, his relatives, and his medical and legal advisors has to be considered, and his reactions in the past to the strains and stresses of life prior to his injury is also of the utmost importance. The fifth and last consideration is the ability of the physician to cause the paralysis to disappear by psychogenic means. This is the proof of all that is gone before and is almost the sine qua non of a diagnosis of hysterical paralysis, for frequently it is only when the patient is cured of his paralysis that one can look back and say that it was of hysterical origin.

In the differential diagnosis, next to paralysis due to injuries of the brain, cord, or peripheral nerves, multiple sclerosis is the more common source of error. The sudden appearance of paralysis in young persons possessed of a personality somewhat similar to that of hysterical persons is often deceiving. The equally sudden and mysterious disappearance of such paralysis makes it even more difficult, and signs of organic disease may be few and uncertain. The emotional control of patients with multiple sclerosis is often poor and the first impression they give is that they are hysterical. Often the long history of remissions and exacerbations inextricably mixed with a highly colored dramatic social existence reads like the story of the stormy career of an ill-adjusted hysterical patient. The differential diagnosis is usually based on the presence of such signs of organic disease as nystagmus, optic nerve changes, the loss of abdominal reflexes, Babinski's sign, and the findings in the spinal fluid. One or more of these are seldom wanting. Occasionally one finds a patient with multiple sclerosis who has embellished his or her disease with some hysterical addition. In one patient seen here there was typical hysterical paralysis of the right lower extremity. The patient dragged the limb nonchalantly after her with the dorsum of the toes scraping the floor, the power in the limb varying enormously from day to day. A few minutes of

persuasion backed up with faradism abolished this disability and thereafter the patient walked with only a slight limp hardly to be detected. Obvious signs of organic involvement of the cord and brain however remained and the spinal fluid was unequivocably that of multiple sclerosis. The ultimate course of the disease corresponded to this latter diagnosis.

TREATMENT

The treatment of these patients is difficult. It is almost a platitude to say that the curing of one symptom of hysteria by abolishing paralysis is not the curing of the fundamental disease. However, in the course of practice the relatives of the patient demand it, and it is only by this means that complete confidence of the patients may be obtained and some improvement made in their underlying ill-adjusted, inadequate personality. Before assuming the responsibility of the care of an hysterical person the case has to be judged very carefully and a wise selection made, for in certain instances the impossibility of accomplishing anything is obvious and failure will reflect discredit on anyone who is taking charge of the case. Medicolegal cases wherein hysterical paralysis has followed some injury during employment and in which the patient is actually engaged in the process of legal action, had better be left strictly alone until the whole case has been settled. The machinery of litigation and the emotional disturbance entailed in the process is sufficient to undo anything that might be accomplished by the well-intending physician who merely seeks to cure the patient apart from any battle for compensation in which he may be involved. It is to be remembered that subconsciously most hysterical persons do not desire to get well, since their paralysis represents the line of least resistance to them, especially when the possibility of any easy competence for life in the form of a huge legal award is anticipated.

During the treatment of the paralysis the patient's care must be assumed by one person alone who is willing to spend time and take the full responsibility. He must gain patients' confidence and obtain full control over their actions by isolating them from all their former troubles, from their relatives, and from the com-

plex play of events in which they have become overwhelmed. It is usually essential to place them in a hospital and keep them from contact with surroundings that influence their weak, easily suggestible minds. With the patient isolated and completely under the control of the physician one of two methods may be adopted to cure the paralysis. One is the sudden and dramatic method whereby the patient is shocked into recovery by some theatrical device. The better one is the slower process of re-education both physical and mental. The patient is assured that there is no organic disease and that recovery is absolutely certain provided full coöperation is given. The cause of the paralysis is explained by stating that the patient has forgotten how to use the limb during the course of the mental stress through which he has passed. A faradic current may be used to cause a contraction of one small muscle in the paralyzed limb, for example, the opponens pollicis. Movement of this apparently paralyzed muscle is demonstrated so that the patient can feel and see it. He is then urged to contract the muscle immediately the current is shut off. Usually a very faint movement follows which is triumphantly exhibited as a sign of recovering power. From then on the same process is followed, each muscle being taken in turn, the physician urging the patient along toward the use of the limb with plenty of encouragement, assurance, and suggestion. The usual course is that very little happens the first few days, when more or less suddenly rapid progress begins and occasionally the complete restoration of function occurs before it is expected. By this process of reëducation the treatment is kept on a sound footing and relapses are less likely to occur than when a sudden restitution of function is attempted. Another point is, that should the sudden method fail the physician is left with no other recourse and is likely to appear somewhat foolish. During the course of these treatments it is possible to reëducate the patient's mind as well as his muscles. Explanation is given of the processes entailed in the production of paralysis. He is led back over the path by which he came, and naturally this involves a reversal of the process of suggestion whereby the paralysis occurred. This counter-suggestion is naturally much

harder to carry out than the morbid one which produced the patient's downfall, since we are dealing with inferior clay. An attempt is made usually to strengthen his philosophy of life and to educate him into facing his individual problem and solving it without falling back, on the easy way out in the form of hysterical paralysis.

SACRAL TUMORS: REPORT OF FORTY-TWO CASES WITH SPECIAL REFERENCE TO THEIR NEUROLOGIC ASPECTS

FREDERICK P. MOERSCH

The conception of this study developed from the fact that frequently patients suffering from "sciatic pains" failed to respond to the usual accepted treatment, and a more careful investigation then revealed the presence of a sacral tumor. Careful routine examination might often have prevented the delayed diagnosis by showing that: (1) in 83 per cent of the cases the tumor could be felt by rectum, and (2) in 37 per cent the roentgenogram contained positive evidence of destruction of bone in the sacral region.

Much has been written with regard to the various phases of sacral tumors, particularly those of congenital origin, but comparatively little has been written from the neurologic aspect of the problem. Steinke, in a statistical study of 330 cases collected from the literature of spinal tumors, makes no specific reference to sacral tumors, while Law in 1922 stated that he could find only thirty cases of anterior sacral tumors reported in the literature. It is undoubtedly true that these tumors are not common, but from our records it would seem that the incidence is higher than was formerly believed. Hundling in 1924 reported nineteen cases from the Mayo Clinic, but discussed mainly the surgical features. Spiller in 1908 mentioned pelvic tumors in his differential diagnosis of cauda equina lesions, while Gordon in 1910 called attention to the frequency of malignant disease of the sacrum simulating sciatica, and reported two cases. Jacobson and also Parker emphasized the point that lesions producing symptoms of caudal disturbance might be in any of four separate and distinct positions, namely, conus lesions, high caudal

lesions, low caudal lesions, and pelvic lesions. Tumors of the latter group, particularly those occurring on the anterior surface of the sacrum, will be discussed here; other pelvic tumors will be considered only in the differential diagnosis.

EMBRYOLOGY

Many observers have come to essentially the same conclusions regarding the embryologic basis for the development of most sacral neoplasms. Briefly stated, the caudal end of the embryo represents a Sargasso Sea, producing as a result of its variegated structures a "histologic potpourri." Whether all sacral tumors have their origin in remaining coccygeal vestiges or other structural anomalies must, of course, remain an open question. Certainly it would seem that congenital sacral tumors are of such embryologic origin. It is also possible that a second group of tumors, the ependymal-cell gliomas, are of such origin, as the cells are of embryonic character, and it may be assumed that they arise from tail nests or coccygeal vestiges.

PATHOLOGY AND GROUPING

Pathologically practically all types of tumors are represented in sacral growths. Borst, who has done a tremendous amount of work on congenital sacral tumors, presents several very plausible classifications. From the neurologic standpoint there is no need of entering into a discussion of classifications, as with it is involved the problem of origin of tumors. The following grouping is given only for convenience of discussion and to show the wide range of neoplasms encountered: (1) dermoid cysts, teratomas, neuroblastomas, chordomas, and tumors associated with spina bifida; (2) ependymal-cell gliomas; (3) carcinomas, sarcomas; (4) fibromas, chondromas, lipomas, myomas, and so forth; (5) mixed tumors, and (6) foreign-body giant-cell tumors. Sacral tumors usually are not malignant, but they produce grave results because of infiltration of the surrounding important structures. Not infrequently metastatic lesions may be found in the sacrum, but metastasis of primary sacral tumors is rare, although in the

presence of carcinoma and sarcoma such a possibility must be kept in mind.

SYMPTOMS

Sacral tumors present a rather uniform syndrome, although individual variations must necessarily occur. A heretofore healthy person becomes aware of a sense of pressure in the rectum or sensitiveness at the end of the spine. Within a variable length of time, usually years, it is noted that the soreness may spread to the buttocks, the bowel movements become difficult, small in caliber, and frequently there is a desire to micturate or defecate without results. The close observing patient will possibly notice a slight numbness about the anus and a tendency for the pains, which had previously been fairly well localized, to radiate to one or the other or to both thighs. Usually at this point a diagnosis of sciatica is made. Occasionally there is a reversal of the symptoms, the sciatic pains appearing first and later the rectal difficulties, particularly if the lesions are of high caudal origin. Rarely is the first evidence of a sacral neoplasm discovered by rectal examination, or, as noted by Law in one case, by obstruction during delivery. With the advent of increasing pain the patient notes a desire to stand, at night his pain may be worse, and, as in cord tumors, he must frequently get up to either change his position or to walk about. In women, as a rule, the tumor is usually discovered earlier as pelvic examinations are made more or less as a routine. In the male rectal examinations are not only more difficult, but are so frequently neglected as a routine procedure that by the time a diagnosis is established the patient has submitted himself to numerous and ineffective therapeutic measures.

Late in the disease process marked spinal rigidity with disturbance of gait, weakness, perianal anesthesia, and incontinence of bowel and bladder are added to the picture. Occasionally, as has been noted, bladder or rectal difficulties may be among the first symptoms. As has been mentioned, the tumor may be discovered accidentally, as during labor, or the patient may have been having vague rectal and sciatic pains for years. In one case of ependymal-cell glioma the patient had complained of

pain for thirteen years before a correct diagnosis was made. If the tumor is carcinomatous or sarcomatous, the history is, as a rule, much shorter, usually from six months to two years. In the case of dermoid cysts the history of recurrence may have extended over twenty-five years or more. Heusner reported the case of a man aged seventy-two who had a large epithelial tumor removed without any previous symptoms, the tumor probably having existed as a dermoid cyst for years. In one of the Mayo Clinic cases a woman aged sixty-seven had a dermoid of the sacrum removed which had been slowly growing for at least thirty years. Mallory reports the case of a woman aged forty-four who had noted twenty-five years previously a tumor about 2 cm. in diameter situated in the median line over the coccyx. Before it was removed it began to grow rapidly, reaching about 7.5 cm. in diameter. Histologically it proved to be an ependymal-cell glioma. The symptoms are usually very mild and confined essentially to the lesion, and not to its associated complications.

DIFFERENTIAL DIAGNOSIS

As is usual with regard to all neurologic problems the history of these tumors should lead the way to a correct diagnosis. The rectal examination is very important, as in early cases it may be the only means of establishing a diagnosis. Therefore the examination should be made as a routine of all patients suffering from sciatic, rectal, or sacral pains. Such an examination is best made with the patient on his back, as the sacral region can then be easily palpated. Roentgen-ray examination must not be overlooked, and it is well to bear in mind that roentgenograms must be carefully studied, since frequently a lesion which later may appear very obvious is overlooked. Special attention must be given to the reflexes of the lower sacral segments. At times no reflex disturbance can be demonstrated. Occasionally the only finding is the loss of an external hamstring response. It is the rule that these patients have a slight or even marked perianal anesthesia. Examination of the spinal fluid in cases of true sacral tumors is negative, and gives little help from a diagnostic standpoint. When the lesion is higher and has extended into the

sacral canal complete black or yellow fluid will be obtained. It is often well to have a spinal fluid examination made in obstinate or atypical cases of sciatic pain, and thus save oneself embarrassment later.

It would be impossible to discuss all the possible factors which might arise in the differential diagnosis of sacral tumors. Sciatica and the various sciatic pains are naturally the most common sources of difficulty. The history and findings are not those of neuritis, but definitely suggest irritative phenomena, and if findings are present tend to be segmental.

Cord tumors, tumors of the cauda equina and conus are often differentiated with difficulty unless definite evidence of a sacral mass is present. If tumors are in the sacrum, symptoms associated with the rectum and bladder seem to appear early; if they are situated higher, they appear later. There is no sharp line between these lesions, for a neoplasm may be both intradural and extradural, and may even erode through the sacrum, and extend into the overlying muscles. In my experience the following factors have presented themselves for differentiation: (1) Toxic infections (herpes zoster, cauda equina neuritis, and so forth); (2) muscular (trauma, strains, psoas spasm, and so forth); (3) bone (arthritis, spina bifida, hip joint disease, tumors of the bone, and so forth); (4) nerve and cord (sciatic pains, trauma, neurofibroma, cord, conus, and caudal lesions, myelitis, spinal syphilis, and so forth); (5) vascular (intermittent claudication, phlebitis, and so forth); (6) pelvic and abdominal neoplasms or inflammation; (7) associated with constitutional diseases (pernicious anemia, arteriosclerosis, and so forth), and (8) congenital anomalies (dermoid cysts, teratomas, and so forth).

Too often a hurried conclusion is reached when more careful study would have established a correct diagnosis. In 20 per cent of a group of forty-three cases an operation directed toward some striking symptom rather than at the cause of the symptom had been performed. Hemorrhoidectomy is the most common of these misdirected procedures; it was performed in this series in six cases to the embarrassment of both patient and physician.

PROGNOSIS

As a group anterior sacral tumors present a fairly favorable prognosis, but as there are various types, no general statement may be made which will include all.

Congenital neoplasms, such as teratoma, are uniformly fatal, as the infants present poor surgical risks for this radical operation. Dermoid cysts, however, are most favorable. In many instances they have existed thirty or more years without marked inconvenience to the patient. If completely removed they will not return.

In the group of ependymal gliomas (sometimes called neuroepitheliomas) the tumors divide themselves into two types, one originating high, probably from some part of the filum terminale, and the other at a lower level, from some "nest" or medullary appendage. In both varieties the history is long standing, from two to fifteen years, the growths are not essentially malignant and do not metastasize. In both cases the gravity of the affection is in the tendency for progressive growth and the proximity of adjacent vital structures. The low-lying lesions may be completely removed with recovery, particularly if operation is performed early in the disease process. The high intradural lesions which extend up and down the canal present a more difficult problem, and only rarely can they be removed completely. There is little to be said about the remaining types of neoplasm, as they follow the course of neoplasms in general.

TREATMENT

The treatment of these lesions will not be discussed here, since treatment is essentially surgical. If surgery is not possible, radium or roentgen ray may often be applied with encouraging results.

GROUPING OF MAYO CLINIC CASES

The forty-two cases observed in the Mayo Clinic were grouped as follows: ependymal-cell gliomas (low-lying ten, high-lying four), fourteen; sacral tumors (type not determined), five; carcinoma, five; sarcoma, two; foreign-body giant-cell tumors,

three; myoma, two; fibroma, one; chondroma, one; congenital tumors (dermoids), five; and metastatic tumors, four.

Several high-lying ependymal-cell gliomas might properly be added to this group, but only lesions are included in which the tumor extended into the sacral canal and showed evidence of erosion of the bones.

Under the heading "type not determined" were included large anterior sacral tumors of which no biopsy was made, but roentgen-ray or radium treatment was instituted at once. Two lipomas and a chordoma might have been added to the series,

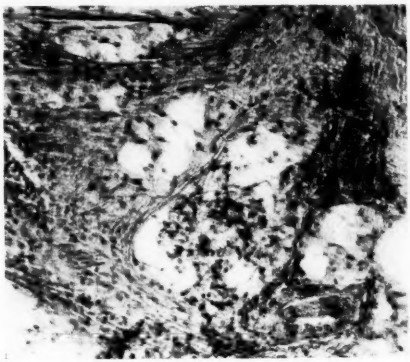

Fig. 98.—Ependymal-cell glioma (× 100).

also several dermoid cysts, but as the records of these cases were not complete, it was thought advisable to omit them.

According to Broders the foreign-body giant-cell tumors are not malignant, but the result of an inflammatory reaction. If entirely removed they do not recur. One patient in the series recovered. In two cases the growth could not be entirely removed and there was recurrence.

Of the cases of metastatic tumor only those were included in which there were no neurologic symptoms associated with the primary lesion, and the sacral metastatic growth clinically appeared to be an anterior sacral tumor. Naturally many other cases might be included in the series, but my chief purpose is to

call attention to the possibility of the metastatic group being confused with primary sacral neoplasms.

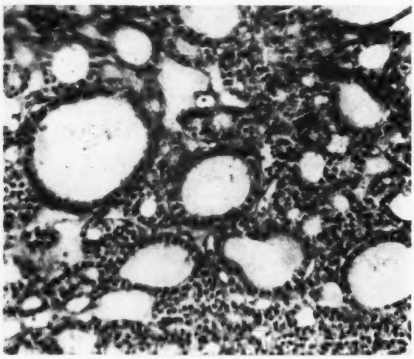

Fig. 99.—Adenocarcinoma (× 100).

The tabulation is included to illustrate the general picture presented by sacral tumors. The remaining tumors might be

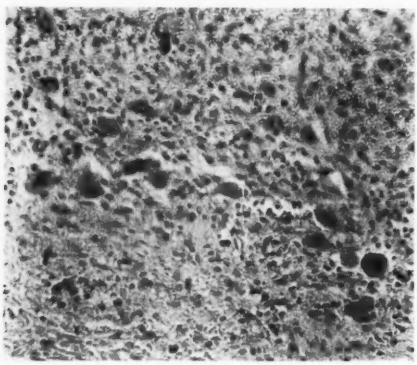

Fig. 100.—Foreign-body giant-cell tumor (× 100).

tabulated in a similar manner, each group having slight variations, particularly with regard to duration and mortality. Figures 98 to 103 are self-explanatory.

TABULATION

Ependymal-cell Glioma

Case.	Age, Sex.	Date.	Symptoms.	Physical findings.	Roentgen-ray findings.	Neurologic examination.	Operation and findings.	Remarks
1	31 M.	January 20, 1916.	Right sciatic pains for last three and one-half years. Diagnosis of arthritis. Returned 5/27/25, same complaint, but more marked.	Negative.	Destruction of fifth lumbar, and first, second, and third sacral vertebræ. Spina bifida occulta.	Achilles' reflexes absent. Loss of all sensation in fourth and fifth sacral segments.	Partial removal of mucoid glioma of sacrum 6/20/25, ependymal-cell glioma.	Roentgen-ray therapy 3/25/26. Condition same thirteen years.
2	68 M.	April 27, 1916.	Pain left leg for past month. Constipation and difficulty in urination.	Sacral tumor, fluctuation posterior.	Destruction of middle of sacrum.	None.	Partial removal of Ependymal-cell glioma 11/28/16. Erosion of sacrum.	Patient died 1/28/18. Intestinal obstruction for six years and three months.
3	47 M.	December 27, 1920.	Pain in rectum last two and one-half years, later pain down legs.	Large pelvic mass fixed to sacrum.	Negative.	Right leg weak. Reflexes normal. Sensory impairment of fourth and fifth sacral segments.	Partial removal of ependymal-cell glioma of the sacrum 1/7/21.	Died September, 1924. Duration six years and three months.
4	65 F.	September 4, 1923.	Pain end of spine for last five years, gradually worse.	Anterior sacral tumor felt by rectum.	Erosion of sacrum.	Some peri-anal sensory disturbance.	Removal of ependymal-cell glioma from sacrum 10/6/23.	Five years to operation.
5	47 M.	July 28, 1924.	Since May, 1924 pain over sacrum and in rectum.	Anterior sacral tumor felt by rectum.	Negative. Destruction of second and third sacral vertebræ.	Disturbance of sensation in fourth and fifth sacral segments.	Partial removal of ependymal-cell glioma of sacrum 5/29/25.	About the same 4/1/26. Duration two years.
6	45 F.	September 14, 1925.	Since September, 1924 pain in right hip. Operation elsewhere November, 1924. Well August 1, 1925.	Large sacral tumor 7.5 cm. in diameter.	Were positive, now negative.	Negative. Sensation (?). Radium burns about rectum.	No operation. Ependymal-cell glioma.	Radium. Fair condition one year and six months.

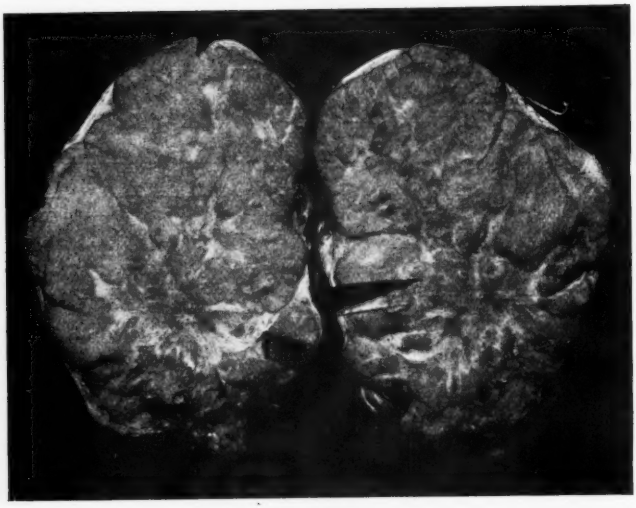

Fig. 101.—Sarcoma.

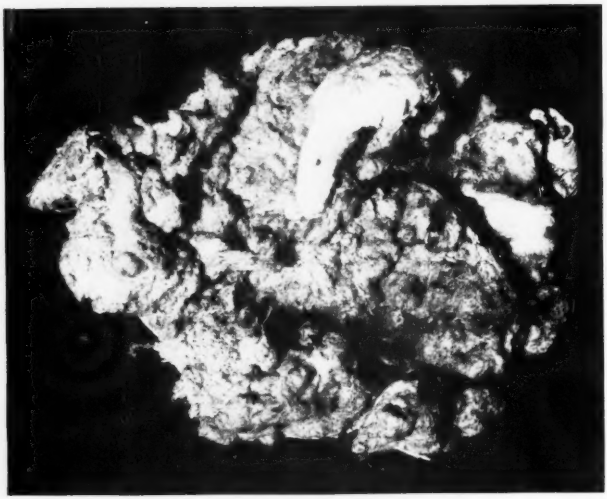

Fig. 102.—Colloid carcinoma (dermoid cyst).

It may be assumed from this rather large group of cases that sacral tumors are not rare. In most cases the early symptoms might well be attributed to neurologic disorders, and careful study usually reveals definite evidence of involvement of the nervous system. The need of careful rectal examination cannot be overemphasized, as in many instances this examination is entirely overlooked and in itself would frequently establish a cor-

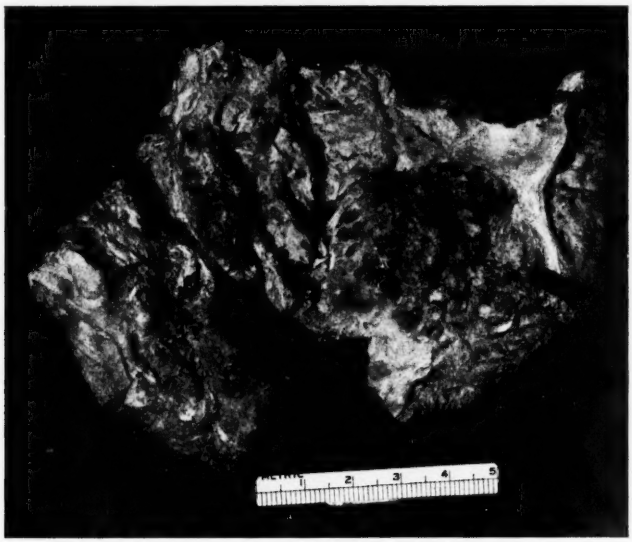

Fig. 103.—Myoma.

rect diagnosis. The fact that these tumors are of such varying types both as regards their origin and structure precludes any generalized statement as to age, incidence, and mortality.

CONCLUSIONS

1. A rectal examination should be made in all cases in which there is rectal, sacro-iliac, or sciatic pain.

2. Roentgenograms are usually negative; careful examination may, however, reveal positive findings in a few cases.

3. There is no history of a true neuritis, but of symptomatic sciatic pains. The early pain may be entirely rectal; sciatic pains appear later.

4. Perianal anesthesia should be diligently searched for.

5. Often unnecessary surgical procedures are instituted for symptoms rather than for the disease process.

6. All types of tumors are found in the sacral region; most of them are congenital in origin, developing from skeletal, medullary, or postanal "rests." Of this group the ependymal-cell gliomas are probably the most common and important.

7. Ependymal-cell gliomas are not malignant, they do not metastasize, but tend to erode their way into surrounding tissue.

8. Ependymal-cell gliomas are slow growing; the history of symptoms in several instances extends over ten years.

9. When possible the tumors should be removed completely or radium and roentgen ray used.

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RELAXED RECTUM A SIGN OF LOCOMOTOR ATAXIA

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For many years I have been interested in the fact that in some men and women the rectum is so relaxed that one can pass a sigmoidoscope its full length into the bowel almost without resistance. Ordinarily, and especially in strong, sensitive men, one has to exercise considerable care and skill in threading the instrument past the valves of Houston and on into the sigmoid, but in these cases the instrument may slip in almost of its own weight. This relaxed state of the rectum may be detected to a certain extent also with the examining finger. Normally the anal ring grips the finger firmly, and the tissues in the pelvis feel fairly firm; but in these cases the whole perineum is so flaccid that it can be moved backward and forward and from side to side.

I kept notes on the patients with this pecularity, and soon found that most of them were tabetics. This was not surprising because it is well known that all the muscles in the tabetic person tend to relax. It is known also that the bladder is often peculiarly trabeculated and that it empties poorly, so it is not strange that the rectum should also be abnormal.

It is too early to say just what proportion of tabetics show this sign because I have not had access to enough material. Through the kindness of Dr. Nixon, I was able to examine a number of the neurosyphilitic patients under treatment at the University of California Clinic, and found that all of those with advanced tabes showed it. Most of those in the early stages of the disease do not show it, but some do, and it may become a helpful sign; in fact, on two occasions it has led me to make diagnoses which I might otherwise have missed. In one of these cases the patient

was a young man of twenty-four who developed diarrhea while in Cuba. On his return to the United States he consulted a number of physicians, some of them specialists, who all treated him for amebiasis, partly because of laboratory reports, but largely because he had been in Cuba. On passing a sigmoidoscope I was astonished to find a greatly relaxed sigmoid. His knee jerks were weak, the Wassermann reaction on the blood was positive, and careful questioning revealed that he had been thoroughly treated for syphilis at the age of seventeen, that his bladder was not functioning properly, and his sexual power was gone. One or two doses of salvarsan immediately cured the diarrhea.

The next question is: Is the relaxed rectum ever present in other disease conditions, or in health? It certainly is. I have seen it in the type of woman with markedly relaxed perineum, who suffers perhaps from prolapse of the uterus in spite of the fact that she has never borne children. I have seen it also in a few cases in which the only explanation seemed to be that there was a long loop of sigmoid reaching almost to the diaphragm. In such cases the mesentery of the sigmoid was probably so free that it was easy to pass the instrument into the bowel.

I have seen a relaxed rectum also in cases of pernicious anemia when it may have been due partly to the changes in the cord, or partly to the tendency to diarrhea. I have seen it in a few cases of diarrhea of unknown origin. It was not present in a man with probably congenital absence of knee jerks. His muscles, however, were well developed and fairly tonic.

I can hardly believe that these observations are new, but a certain amount of search through the literature and conversations with a number of neurologists and proctologists have shown me that the sign must be known, if at all, to very few. The reason for it is doubtless that neurologists do not pass sigmoidoscopes and proctologists are not much interested in tabes.

The subject would seem to be worth investigating further because hardly a month passes that a busy clinician is not called on to rule out the early stages of neurosyphilis, and any extra signs of the disease should be welcomed.

In passing it might be well to call attention to another peculiar type of relaxation of the rectum which can be seen in cases of carcinoma of the rectosigmoid. Ordinarily when one inserts the finger into the rectum, one realizes that the walls are collapsed, but if there is a carcinoma just beyond one's reach, one will often get the feeling that the finger is moving freely in a cavernous space. This sensation, when once experienced, is quite striking and not easily forgotten. It should warn the examiner not to omit the proctoscopic examination.

CAROTINEMIA

CARL H. GREENE AND L. MINOR BLACKFORD

The characteristic bright yellow of butter made in June as compared with the paler winter product from hay-fed animals is familiar to all. The farmer has learned that the color and therefore the market value of butter can be maintained in winter through the judicious feeding of carrots or pumpkins to the dairy herd. The color of egg yolk can be increased by similar dietary adjustment. One hundred years ago Wachenroder first isolated a crystalline, lipoid-soluble pigment from carrots, but it remained for Palmer and Eckles to identify this plant pigment, carotin, as the chief pigment responsible for the color of butter-fat and beef serum, and to show the relationship between the diet and the amount of the pigment present. Palmer and Kempster made similar studies of the allied xanthophyll or carotinoid pigments in fowls. The chemical and physiologic behavior of these pigments has recently been summarized by Palmer.

The significance of the carotinoid pigments in metabolism, if any, has not been discovered. They are apparently of exogenous or dietary origin. Palmer and Goebel and Stern believe that they play no definite rôle in the nutritional and metabolic processes, at least of the higher animals, but van den Bergh and Muller do not wholly accept this conclusion. Miyake, who has made extensive physiologic investigations, found that carotin is liberated during the course of digestion both in the stomach and intestines and that some is absorbed from the intestines. Excretion occurs primarily through the colon and epidermis, although small amounts can be excreted in the urine. This was previously suggested by Hess and Myers, although denied by Kohn and Hashimoto.

The list of dietary substances furnishing carotinoid pigments is extensive: Carrot, pumpkin, yellow squash, yellow turnip, parsnip, spinach, green or yellow beans, kale, orange, and egg are the most commonly named. A diet containing enough of these foods to cause carotinemia must be predominantly vegetable. These pigments, if ingested in sufficient quantities, may cause staining of the blood serum and skin in man as well as in the domestic animals.

Von Noorden in 1904 called attention to a characteristic canary yellow pigmentation of the nasolabial folds, palms and soles, with white sclerotics, occurring in certain cases of diabetes. He believed this to be a manifestation of diabetes and termed it "xanthosis diabetica." Umber, Minkowski, Lubarsch, Head and Johnson, and Niehaus later reported similar cases. Van den Bergh and Snapper in 1913 particularly pointed out the presence of the so-called lipochromes in human serum and that the greatest amounts were found in diabetic patients in whose skin there was a yellowish pigmentation. Later Bürger and Reinhart, using the spectroscope, identified carotin and xanthophyll in the serum of nine diabetic patients on diets containing much green kale or spinach. They further noted that it was not found in untreated patients and that changing the diet changed the amount of xanthosis. These observations suggested the exogenous origin of the pigments.

Moro in 1908 experimented with carrots as a supplementary food in certain types of nutritional disturbances in infancy and observed that some of the children became subicteric. This observation was later confirmed by Kaupe, Stoeltzner, Klose, and Salmon. The earlier observers apparently considered the pigmentation abnormal, but Salmon identified this pseudo-icterus with the xanthosis diabetica of von Noorden. Further cases in children have been reported by Hess and Myers, who first used the term "carotinemia," and by Ryhiner, Kohn, and Goebel and Stern.

The Japanese literature also contains references to a yellow pigmentation of the skin from eating oranges or yellow squash. According to Hashimoto and Miyake, this was first described by

Baeltz in 1897, under the name "aurantiasis cutis." It does not appear to have been associated with diabetes. The Japanese observers recognized the dietary origin of the condition, noted the deposition of the pigment in the horny layer of the skin, and established the identity of aurantiasis cutis with carotinemia.

Perhaps the first case of carotinemia reported was that of Hayem, at least the description of the pigmentation is typical, although he considered it to be a case of icterus. There was no note as to the diet. Salomon spectroscopically identified as carotin the pigment found in the serum of normal adults living on a diet rich in carotinoids. Burger and Reinhart, Schüssler and McGill reported cases in non-diabetic adults.

Hess and Myers observed a yellow pigmentation of the skin in two otherwise normal children receiving a daily ration of carrots, and proved the presence of carotin in the serum. They were able to reproduce the condition in infants by feeding two oranges, an egg, or two ounces of spinach, daily for a month. They noted, as have Kaupe and others, an individual variation in susceptibility to the accumulation of carotin in the serum. It is possible that this susceptibility may be increased in diabetic persons. Miyake was able to duplicate the experiment of Hess and Myers in an adult. One subject ate 1200 oranges in a period of six weeks, and the presence of carotin in the blood serum was demonstrated. Bendes has recently made practical use of the condition as an aid in heliotherapy among tuberculous children. Dark-skinned children were readily tanned by the sun and thereby benefited, whereas the blond ones were blistered repeatedly. Darkening the skin of his blond patients by means of a vegetable diet before exposing them to the sun facilitated tanning and good results with heliotherapy.

The appearance of patients with carotinemia is characteristic. The diffuse yellow pigmentation of the skin is most marked over the palms of the hands, the soles of the feet, and in the nasolabial folds. Palmer and Kempster found the carotinoid pigments in fowls to be chiefly deposited in the rete malpighii and the cornified layers of the epidermis, especially the latter. Similar observations have been made in man by the Japanese observers

who also report the presence of pigment in the sebaceous glands. These findings explain the distribution of the pigmentation and especially the intensification of color in callouses in the palms, or exposed areas where the skin is thick and rough, as on the knee or elbow. The presence of sebaceous glands, on the other hand, explains the intensification of color in the nasolabial folds and the axillæ. The sclerotics are clear, this being one of the striking differential points from a true icterus. Miyake in one instance described pigmentation of the gums, palate, and conjunctivæ perhaps from staining of the subcutaneous fat. This should be recognized as unusual and characteristic only of the extreme cases. Usually the mucous membrane is free from staining, again contrasting with the condition in jaundice.

The bright yellow is usually described as a lemon, ochre, or golden, depending on the intensity. The brown or green tint of the skin so frequently observed in jaundice is absent. Similarly the serum is yellow, or, if the carotinemia is marked, orange, while in obstructive jaundice, particularly in long standing and in malignant cases, the serum may be slightly but characteristically greenish from the presence of traces of biliverdin.

The demonstration of the pigment in the blood serum, which is a deeper yellow than normal, is relatively simple. The color measured against standard bichromate solution as used by Meulengracht, Stetten, Bernheim, and others gives a high icterus index, while the amount of serum bilirubin is not increased. That the color is due to carotinoid pigments can be shown by adding 2 c.c. each of alcohol and petroleum-ether to 2 c.c. of the serum, and centrifuging the mixture. The protein precipitate is left colorless, the pigment passing into the upper layer of petroleum-ether. Comparing this latter with the bichromate standard will show that the greater portion of the serum pigment has been extracted. The presence of carotin or xanthophyll can then be demonstrated spectroscopically or by the chemical tests outlined by Palmer or Miyake.

Most observers have confined themselves to the demonstration of carotinoid pigments without further analysis. In the case of Head and Johnson carotin was the sole cause of the pigmenta-

tion of the serum and skin. The patient had diabetes and carrots were an important part of the diet. In another case, studied by Palmer, with a diet rich in eggs and green beans, there was little carotin but much xanthophyll present.

Carotinemia has often been noted in the Mayo Clinic in cases of diabetes.[34] It has been noted much less often in other cases, but during the last five years thirteen cases have been observed without the presence of diabetes. Although the condition is of little metabolic significance, the circumstances under which it may arise and the possibility of confusion in diagnosis warrant the discussion of the following cases.

REPORT OF CASES

Case 1.—A physician, aged forty, had discovered that he had diabetes mellitus six years previously. The principal finding was glycosuria, which he was readily able to control through a diet of vegetables in which spinach figured largely. He had gradually developed yellowish pigmentation of the skin, more noticeable on the exposed surfaces, and it was on this account that he came to the Mayo Clinic.

Physical findings were essentially negative save for the yellow color of the skin, more marked on the palms and soles. The sclerotics were clear. The blood pressure and the hemoglobin were normal and studies on the morphology of the blood were negative. Roentgenologic examination of the stomach and gallbladder were also negative. The fragility of the blood corpuscles was normal. The blood contained 0.100 per cent of sugar and 0.166 per cent of neutral fat. The orange pigment of the serum was entirely extracted with petroleum-ether. On change of diet the pigmentation disappeared.

Case 2.—A man, aged thirty-eight, had suffered for about a year with continuous mild epigastric pain, severe dyspepsia, and bloating after meals. He was relieved by food or soda. He had had three attacks of colic referred to the right hypochondrium in the preceding six months, in the last of which he had required morphin. The pain did not radiate to the back or shoulder. He had made no consistent effort to diet.

Physical examination revealed yellowish, rosy skin, suggestive of that in diabetes. It was not the yellow of jaundice, but more like carotinemia. There was spasm of the abdominal muscles over both the gallbladder and appendix. The blood sugar was 0.11 per cent. At operation the stomach and duodenum appeared normal. There were no stones palpable in the gallbladder, although its walls were slightly thickened. The appendix was found subacutely and highly inflamed, and considering the condition of the appendix sufficient to explain the trouble, the surgeon removed it. The patient was well more than two years later.

Case 3.—A man, aged thirty-three, had been subject to headaches, bilious spells, and constipation for more than ten years. He had not been well since a severe attack of influenza in 1919, although he had not had to give up work during the intervening seven years. A chronically inflamed appendix had been removed elsewhere in 1923. For two or three years he had had a dull pain in the lower left quadrant of the abdomen after eating heavy foods. Six months previously he had become a vegetarian. Besides eating a great deal of spinach he sometimes ate carrots three times a day. In this time he had lost about 35 pounds, had become weak, and was alarmed because of the yellow color of his skin.

Although fairly well developed and nourished, neurotic traits were very prominent. The yellow tint of the skin was most marked over the hands, feet, axillæ and groins. The red blood corpuscles were of normal fragility and there was no anemia. Gastric acids were normal and roentgenologic examinations of the gallbladder and stomach were negative. The blood sugar content was 0.10 per cent and the serum contained 1 mg. of bilirubin for each 100 c.c. by the indirect reaction of van den Bergh. Petroleum-ether dissolved a yellow pigment from the serum. The headaches were attributed to migraine, and the loss of weight and strength to inadequate nutrition.

Case 4.—An introspective bachelor, aged forty-nine, had lived alone on a farm. He had had intermittent, vague abdominal discomfort for thirteen years; it had been more or less constant for ten months and consisted essentially of periodic spells of anorexia, a sense of epigastric fulness and bloating after eating, and some discomfort in the iliac fossa. Dilute hydrochloric acid gave relief for a time. In seeking to overcome his distress he had eliminated almost everything from his diet except fruits and vegetables. For several months he had eaten carrots almost daily. He came to the Mayo Clinic because some weeks previously he had noticed a yellowish discoloration of the skin, particularly of the palms. There was no history of colic or clay-colored stools.

The yellowness of the skin, the white sclerotics, and a right inguinal hernia were the outstanding features of the physical examination. There was achlorhydria, but the hemoglobin and blood counts were normal. A roentgenogram of the spine revealed hypertrophic arthritis. Roentgenologic examination showed a normal stomach. Blood fats 0.433 per cent and blood sugar 0.084 per cent were found. During the two weeks the patient was under observation on a normal diet the pigmentation of the skin faded.

Case 5.—A man, aged thirty-three, had grown fat while eating heavily of sweets. Urinalysis two years before had showed sugar, which disappeared on modification of the diet. His ambition led him to add to his usual work of eight hours as a clerk much work at night along different lines during which time he made a successful invention. He ate rapidly and irregularly and took no vacations. His labors brought him promotion with additional responsibilities, which were still further increased by matrimony a year before he came to the Clinic. Sexual excesses ensued. Four months earlier he began to suffer from lassitude and loss of weight, which attracted remarks from his

friends. For the last three weeks he had been eating a raw carrot daily and had observed a yellow tinge to his hands and feet.

The color of the skin and infected tonsils were the only items of interest noted on physical examination, and this color and worry over the lassitude and the loss of weight were his only complaints at this time. The hemoglobin and gastric acids were normal. Blood sugar was 0.109 per cent. Roentgenologic examination of the stomach and a study of the morphology of the blood were negative. It was interesting to note that his wife's skin was similarly although less markedly pigmented. While they were under observation the color faded away.

Case 6.—A man, aged forty-five, was frankly psychoneurotic, and had been unable to succeed in anything. In seeking an organic basis for his failures he had consulted many physicians as well as many quacks. He believed that an imperfect digestive system prevented the elimination of certain poisons, and had therefore confined himself to a diet of vegetables in which carrots figured largely. Six months previously his gallbladder had been drained medically on account of generalized yellow pigmentation. The bile so obtained was normal, but the patient felt that he was being benefited and prevailed on his physician to continue the drainage for a time. However, he finally lost hope of permanent cure and discontinued the treatment.

The skin, with the exception of the palms and soles, which were orange, was a bright yellow. The sclerotics were clear. Dental sepsis was present. Roentgenologic examination of the stomach revealed no lesions, although achlorhydria was present. The blood showed slight secondary anemia which was attributed to faulty diet. The blood sugar was 0.075 per cent; the tolerance curve normal. The icterus index of the serum was 14, but all of the pigment was extracted with petroleum-ether. The color faded perceptibly during the week that the patient was under observation (Table 1, page 740).

DISCUSSION

Apart from the cases in which carotin-rich diets were taken experimentally with the idea of producing carotinemia, the various types of cases in which this condition occurs in adults are illustrated in the present series. The form first described as diabetic xanthosis is well illustrated in Case 1. The diabetes was controlled by a diet of 5 per cent vegetables in which spinach predominated. Although in such vegetables as carrots or pumpkins the presence of carotinoid pigments is obvious, this case emphasizes the fact that the chlorophyll in green vegetables, such as spinach, may mask equally great quantities of yellow pigment. Case 2 is of especial interest as illustrating the presence of definite chronic abdominal disease, with a history strongly suggestive of cholecystitis. In Case 3 the color of the skin, the

TABLE 1

SUMMARY OF CASES*

Case.	Age, years.	Sex.	Chief complaints.	Dietary history.	Degree of pigmentation.	Diagnosis.
1	40	M.	Yellow skin and diabetes.	Spinach six years.	3	Controlled diabetes mellitus.
2	38	M.	Indigestion and epigastric pain.	No note.	(?)	Appendicitis.
3	33	M.	Weakness, weight loss, pain left side.	Vegetable diet, carrots three times daily and spinach.	2	Migraine, neurosis.
4	49	M.	Yellow skin and indigestion.	Carrots daily for months.	3	Neurosis.
5	33	M.	Yellow skin and weight loss.	One raw carrot daily several weeks.	2	Nervous exhaustion.
6	45	M.	Nervousness and indigestion.	Vegetable diet with much carrot.	3	Achylia, neurosis.
7	46	F.	Indigestion and nervousness.	Carrots and other vegetables, orange juice seven weeks.	3	Neurosis, menopause.
8	56	F.	Cholecystectomy elsewhere.	Carrots daily four months.	1	Neurosis, cholecystitis.
9	52	M.	Indigestion.	Eggs to excess.	2	Latent syphilis, neurosis.
10	64	M.	Headaches with vomiting.	No note.	1	Migraine, incomplete.
11	46	M.	Indigestion and weakness.	No note.	2	Neurosis.
12	16	F.	Asthma and hay-fever.	Orange juice and eggs, particularly fond of carrots.	2	Asthma and hay-fever.
13	31	M.	Stomach trouble.	Spinach and carrots two or three times a day.	2	Gastric neurosis.
14	56	M.	Epigastric pain.	Carrots and spinach.	3	Gastric neurosis.

*In five cases the color grew less under observation and in one (Case 9) was gone on subsequent examination.

The roentgen-ray examination of the stomach was negative in all cases reported; for Cases 7, 10, and 12 no report was given. The roentgen-ray examination of the gall-bladder was positive in Cases 8 and 10, and negative in Cases 2, 3, and 11.

The Wassermann reaction on the blood was negative in thirteen patients, the Wassermann reaction on the blood and cerebrospinal fluid was very strongly positive in Case 9. There was no bile pigment or sugar in the urine of any case.

"bilious attacks," and the loss of weight were sufficient to warrant a second abdominal operation. More careful study revealed the history of migraine, an inadequate diet including excessive amounts of carrots and spinach, and the presence of carotin in the serum, which were sufficient to explain the condition of the patient. Case 4 is an example of the type in which circumstances and especially poverty, as in central Europe after the war, have limited the diet to the coarser vegetables, such as carrots, rutabagas, or squash. Cases 5 and 6 are illustrative of neurasthenic individuals of differing grades of intelligence.

In this series carotinemia was observed at least ten times in patients with marked evidence of chronic nervous exhaustion, although otherwise organically well. McGill's case of carotinemia developing as a result of dietary idiosyncrasy in a patient with definite psychosis represents an extreme. In the neurotic group particularly, the recognition of carotinemia is important, for such persons are subject to a multitude of functional gastrointestinal complaints that may simulate those of chronic cholecystitis. Three of our group came to the Clinic principally because of the yellow skin and suspected jaundice. Three came because a diagnosis of cholecystitis had been made without recognition of the source of the pigmentation (Table 2, p. 742).

In this series of cases the icterus index varied between 7 and 22. The normal index varies between 3 and 5, so that this value suggests the presence of icterus. In all cases studied, however, the serum bilirubin was normal[8] and the urine was free from bile pigments. Jaundice was thus eliminated as a factor in the diagnosis. In these cases the discrepancy between the values for the icterus index and the serum bilirubin can be used as a measure of the degree of carotinemia.

SUMMARY

The occurence of carotinemia in diabetic patients who have been for some time on a vegetable diet is not infrequent. Its occurence may also be noted in those who are poor and consequently consume little but the coarser vegetables, as in Germany during and after the War, but this is rare in the United States.

TABLE 2

SERUM PIGMENTS

Case.	Icterus index.	Serum bilirubin (mg. for each 100 c.c.),	Carotin.
1.....	26	1.1	+
3.....	14	1.0	faint
4.....	18	0.5	+
6.....	14	0.5	+
8.....	8	0.3	faint
10.....	8	0.9	+
11.....		0.6	+
12.....	15	0.3	+

The present vogue for spinach and carrots in feeding infants and children will produce the condition if they are susceptible. The most striking point in the cases reported here is the prevalence of neurosis, which was responsible in great part for the selection of the pigment-producing diet.

Carotinemia is not an uncommon condition. Once recognized and its dietary origin established, it is without further clinical significance. Because of its frequency in diabetic patients, when carotinemia is found, diabetes should also be suspected. The possibility of confusion with jaundice must also be borne in mind. Although the color of the skin and of the serum favors such confusion, the clear sclerotics and the normal amount of serum bilirubin, the normal phenoltetrachlorphthalein test, and the absence of bile pigments in the urine will exclude true jaundice. The history of a diet rich in carotin, the characteristic distribution of the pigment in the skin, and the demonstration of it in the serum are enough to establish the diagnosis of carotinemia.

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THREE CASES OF TULAREMIA

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We are fortunate this evening in being able to present before you these three patients with tularemia, all of whom happen to be under treatment at the Clinic. These are the first cases of this more or less rare disease which have been seen here.

REPORT OF CASES

Case 1.—The patient, a ranchman, aged thirty-three, came to the Clinic July 19, 1926 from northeastern Wyoming near Hulett, for the purpose of learning whether he would have to be operated on for gallstones, symptoms of which he had had for three years. He had suffered a rather typical attack of gallstone colic a week before, which caused him to make the trip to the Clinic at this time. His past history is of no interest except that which concerned a febrile illness from which he was convalescing on admission. May 10 he had been bitten by a wood tick on the inner side of the left knee. He would have forgotten this, since it was a common occurrence, if he had not chafed the site of the bite daily while riding horseback. The site became slightly swollen and red. For three days previous to May 18 he felt tired and listless, and on that day noticed that in walking there was soreness in both groins. That night a high fever was accompanied by prostration and general pains and the glands of the groin were tender and swollen. Thereafter he was delirious for ten days, the temperature several times reaching 106° F. The glands in the left groin continued to swell, while those in the right disappeared. Within forty-eight hours after the onset of the illness the site of the tick-bite became swollen and developed into a round "sore" with a dark red border, from which a "core worked its way out" within a week, leaving a punched-out ulcer the diameter and depth of a fifty-cent piece, on which a crust formed. The fever gradually reached normal in three weeks, but there was an afternoon rise for two weeks longer. The patient had lost much weight and was very weak. After he was up and around, what apparently was a toxic erythematous rash made its appearance and lasted two weeks. The swollen glands remained sore and, after poultice had been applied, began to soften, one breaking down and another being lanced by a physician.

On examination here the patient appeared weak and thin. Although 6 feet tall he weighed only 158 pounds; his normal weight had been between 165 and 170. The systolic blood pressure was 124 and the diastolic 72; the

pulse rate was 80, and the temperature at 4:30 p.m. 99° F. The teeth appeared good and showed no roentgenologic evidence of periapical infection. The tonsils had been removed in 1919. The apices of both lungs presented relative dulness, increased tactile fremitus and harsh breath sounds, and a roentgenogram of the chest revealed bilateral pulmonary tuberculosis, which was apparently inactive; two examinations of the sputum failed to reveal bacilli of tuberculosis. Two fluctuating masses, each about 5 by 3 cm., were present

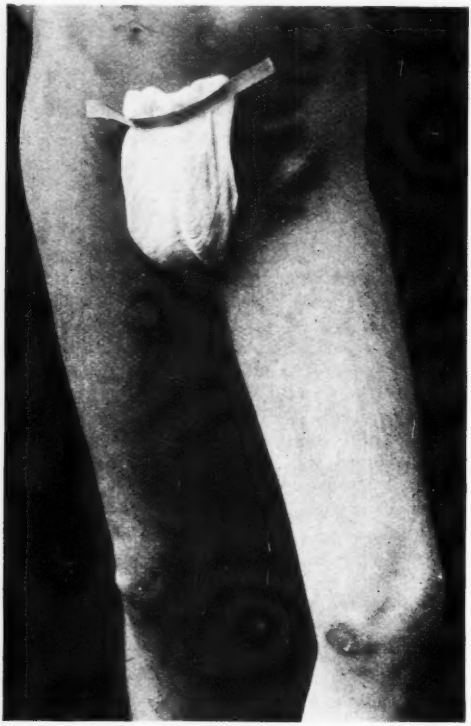

Fig. 104.—Case 1. Adenopathy which followed the bite of a tick.

in the left groin (Fig. 104), and there were two small openings lower which were draining a yellowish serum. These two abscesses were incised in the Clinic one week later and are still draining slightly at the end of four weeks. On the inner side of the left knee was found a round puckered scar about 1.5 cm. in diameter with a dark purplish areola. This was the site of the tick-bite (Fig. 105). The urine was reported normal. There was 73 per cent homoglobin; erythrocytes numbered 4,360,000, and leukocytes 9,200. The

Wassermann test was negative. Roentgenologic studies of the gallbladder by the Graham technic gave evidence of cholecystic disease. Smears and cultures of the draining serum showed no organisms. A blood serum agglutination test was completely positive with *Pasteurella tularensis* antigen in a

Fig. 105.—Case 1. The site of the tick bite, right medial surface of the knee.

dilution of 1:320. The patient is to be sent home to convalesce from his tularemia preparatory to cholecystectomy.

Comment.—This patient tells us that the jack-rabbits are dying off by hundreds in his part of the country and that the wood ticks are very numerous. Seven persons whom he knows have suffered with a disease similar to his and he has heard of other cases in the vicinity. His physician called these cases by the common appellation "tick-fever," but was evidently quite aware that they were tularemia, as the newspapers were warning against the disease. Our patient asserts that a similar plague descends on the rabbits about every ten years. One woman acquired the disease by cutting her hand while cleaning a rabbit, and a man was supposed to have contracted it by eating a sick rabbit, though this method of infection has not been proved.

The others evidently acquired it through the medium of a tick-bite, as this patient did.

Case 2.—The second patient is a farmer, aged forty-four, from Lovell, in the northeastern part of Wyoming. About the middle of June he was bitten on the left side of the face just in front of the ear by a deer-fly, which he quickly killed by slapping with his hand. Two or three days later he noticed a tender enlargement about the size of a "marble" in front of the ear and another such swelling beneath the jaw. At the same time the left eye became swollen, red, and painful, and contained a little pus. He began to feel ill, increasingly so as time went on, and in a few days began to have chills. For two weeks he had fever and in that time lost 23 pounds in weight. As the left eye had become much worse, he called his family physician, who suggested that he might have tularemia and sent him to a nearby ophthalmologist. Several physicians saw him with the ophthalmologist, but could not agree as to the cause of the conjunctivitis and iritis. The general feeling, however, was that it was sympathetic ophthalmia, as the patient gave a history of three pieces of steel having entered his right eye two years before, two of which had been removed surgically, the other having been left in the eyeball. Since then the eye had occasionally become slightly red. As the consultants could arrive at no decision the patient was sent to the Clinic for further study. The day he left home blood was drawn and sent to the hygienic laboratory at Washington for a tularemia agglutination test. The day he arrived at the Clinic a telegram was received stating that the blood showed a positive agglutination with *Pasteurella tularensis* antigen in a dilution of 1:40.

The patient has always been well, the only illness having been influenza in 1918 and an operation for an appendiceal abscess eleven years ago. He has seven children living and well. His family history is unimportant. He uses alcohol and coffee in moderation. August 5 the ophthalmologic report was as follows:

Right eye: Lids and lacrimal apparatus normal; slight reticulate injection of the palpebral and bulbar conjunctiva; some large conjunctival vessels leading up to the limbus on the nasal side; a depressed scar in the sclera below the limbus as the result of a previous operation for removal of two pieces of steel; cornea clear; anterior chamber shallow; iris light blue and apparently bulging forward slightly; pupil 2 mm. in diameter, occluded by a white exudate and seemingly bound down to the limbus; tension −2 to palpation; ocular movements normal; fundus not visible; a foreign body apparently in the sclera in the posterior part of the globe shown by a roentgenogram.

Left eye: Lids and lacrimal apparatus normal; a very diffuse brick-red injection of the palpebral conjunctiva and a slight roughening of the surface; many injected blood vessels in the ocular conjunctiva, especially in the exposed part; a faint central scar in the cornea; anterior chamber of normal depth; iris deep blue; pupil 7 mm. in diameter, inactive to light and accommodation; tension normal; ocular movements normal; fields normal to rough test; internal media clear; fundus negative.

The patient was 5 feet 11 inches tall and weighed 200 pounds, which is his normal weight. Acute tonsillitis and coryza present on admission, afterward subsided, although the tonsils remained chronically infected. There were several carious teeth and a mild grade of pyorrhea. The heart, lungs, and abdomen were apparently normal. The systolic blood pressure was 140 and the diastolic 100; the pulse rate was 80, and the temperature 98° F. The urine was normal except for an occasional leukocyte. Hemoglobin was 73 per cent, erythrocytes numbered 4,770,000, and leukocytes 6,600. The Wassermann test was negative. A roentgenogram of the chest revealed no abnormality. Examination of the prostate as a focus of infection was negative. The blood serum gave a completely positive agglutination with *Pasteurella tularensis* antigen in a dilution of 1:40. The conjunctivitis has nearly disappeared. The removal of tonsils and the enucleation of the right eye in the near future was advised as preventive measures.

Comment.—In this case the infection was probably not due to the bite of the deer-fly on the cheek as the patient thought, for there was never any evidence of an ulcer at that point; it is more plausible to assume that when he killed the fly on his face some of the juice spattered into his eye. It is interesting to note that a week previous to the bite of the fly he took a jack-rabbit away from his dog who had caught it, which is good evidence that the rabbit was sick.

Case 3.—This man, a farmer, aged fifty-three, came to the Clinic August 11, 1926 from Arvada, in the northeastern part of Wyoming, about 200 miles from the home of the second patient presented. His complaint was "eye trouble and diabetes," from which he had been suffering for three months. May 9 he had had a slight chill. The next day he noticed an irritation of the right eye and his wife removed from the inner surface of the upper lid what appeared to them to be the back of a wood tick. This did not seem strange, as he had been accustomed to remove ticks from some pet calves and squash them with his fingers, and he considered it quite likely that a piece of an engorged tick might have flown into his eye. The morning after this event he felt a tender "cord" down the right side of his neck behind the ear, and that night he had a severe chill. He was then delirious for about thirty-six hours. When he recovered from this state he noticed that there were large, painful and tender swellings in front of the right ear, at the angle of the jaw, and beneath the jaw. The right eye was puffed, red, and very painful. He arose from bed, although feeling quite ill, and thinking he had contracted "grippe which had settled in his eye," began to take laxative acetylsalicylic acid. However his eye continued to get worse, and in a few days he went to his family physician, who treated the eye for a brief period and then sent him to an ophthalmologist in a nearby town. The latter described the condition at that time as clinically gonorrheal conjunctivitis with extensive

chemosis and beginning corneal ulceration. The patient was admitted to a hospital in Wyoming May 22 and given intensive treatment; the right eye, however, grew progressively worse, and according to the patient the infection was spread to the left eye by careless nursing. The infection went on to corneal ulceration. Local treatment was powerless to affect the course of the disease, the armamentarium including acriflavin, argyrol, protargol, bichlorid ointment, atropin, dionin, and cauterization of the ulcers, together with injections of milk, mercurial inunctions, mercurous chlorid rubs, and hot packs. As a blood sugar estimation requested haphazardly was reported to be high, the patient was given insulin, and the left eye improved; the right eye had in the meantime suffered corneal perforation. However, there was never glycosuria. The patient stated that during the time he was receiving the insulin he frequently became nervous and shaky, perspired freely, and suffered from tachycardia, all of which symptoms were relieved by eating sugar. After leaving the hospital July 10 he was given insulin by his wife until August 9, the day of his departure for the Mayo Clinic. During this time escape of aqueous humor from the left eye was reported twice. Data regarding his temperature were inaccurate, but he maintains fever persisted intermittently for a month after the onset of the illness. He had had malaria and typhoid fever years before, gonorrhea at the age of seventeen, and a mild attack of influenza in 1919. He used tea, coffee, and tobacco in moderation. He had offspring by each of three wives. He was 6 feet 1½ inches tall, weighed 196.5 pounds against a normal weight of 225 pounds, and felt weak. He wore dark goggles because of photophobia, and could see very little.

The systolic blood pressure was 120, and the diastolic 90; the pulse rate was 80, and the temperature 98.2° F. The right preauricular gland was enlarged and measured 2 by 1.5 cm.; the gland at the angle of the jaw was similarly enlarged, and there was a right submaxillary swelling about 3 cm. in diameter; all were tender, but did not fluctuate. Moderate arteriosclerosis was present. The muscle tone of the heart was weak and the aortic second sound ringing and accentuated. The prostate was enlarged, fibrous, and smooth. The urine was normal except for an occasional leukocyte. The hemoglobin was 80 per cent, the erythrocytes numbered 5,020,000, and the leukocytes 8,000. The Wassermann test was negative. A roentgenogram of the chest showed an old calcified lesion opposite the left fourth and fifth interspaces. Two infected teeth were shown by roentgenogram. The blood sugar was 0.1 per cent and the glucose tolerance curve was normal. There was, therefore, no laboratory evidence of diabetes, and no clinical symptoms of that disease were manifested. An agglutination test with *Pasteurella tularensis* antigen, performed the day of admission, gave a completely positive agglutination in a dilution of 1:320. The ophthalmologic report was as follows:

Right eye: The lid margins are reddened and slightly swollen; there is diffuse redness of the palpebral conjunctiva of the upper lid about 1 cm. from the inner canthus; on the palpebral conjunctiva of the upper lid there is a whitened scarred area, probably the scar of a previous ulcer (the place from which the back of the tick was removed?). There is marked injection of the ocular conjunctival vessels and some circumcorneal injection, staphyloma of

the cornea, fusion of the iris and cornea into one compact mass, and scarring of the entire cornea with large perforations about the center, the iris seemingly being exposed directly to the outside. Intra-ocular tension is normal and ocular movements normal (Fig. 106).

Left eye: The lid margins are slightly reddened. There is moderate reticular injection of the palpebral conjunctiva and a very small amount

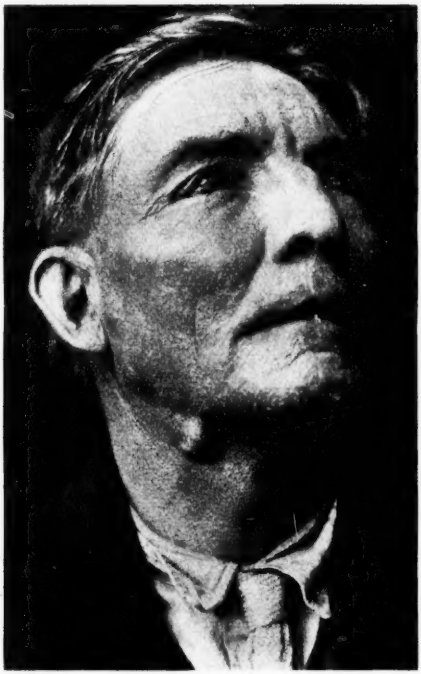

Fig. 106.—Case 3. The glandular enlargement in the neck and ulceration of the cornea.

of serous discharge. The conjunctival and circumcorneal vessels show moderate injection. There is a dense scar over the entire lower half of the cornea, part of the scarred area staining lightly with fluorescein and slight haziness of the upper part of the cornea. The anterior chamber is of normal depth. The iris is slightly muddy in appearance; the pupil is about 5 mm. in diameter and inactive to light. Intra-ocular tension is normal and ocular movement normal.

Comment.—Several cases similar to the last two have been reported from various cities since 1914, when Vail first isolated *Pasteurella tularensis* (then called *Bacterium tularense*) from the eye of a patient. Unlike the previously reported cases, our last patient has recovered with great visual impairment. He now has probably as good vision as he ever will have, which is just enough to allow him to find his way about during the day. As in the other two cases, this patient states that the jack-rabbits have been dying in large numbers in his neighborhood.

DISCUSSION

Edward Francis proposed the name tularemia in 1921 as a technical international name to denote a specific infectious disease due to *Pasteurella tularensis* (McCoy and Chapin). The disease, while natural to many rodents, is incidentally transmitted to man by the bite of an infected, blood-sucking insect or by handling infected rodents.

McCoy and Chapin first isolated and named the organism in 1911 while investigating a plague-like disease in ground squirrels. The organism is a very small nonmotile, Gram-negative rod, growing in minute viscous colonies on artificial mediums. While it grows best on an egg-medium, it will grow well on serum and blood-glucose-agar. The growth is slow, eight days often elaps ing before the colonies appear. The name "tularensis" was used because of the finding of the organism in Tulare County, California, where a large bulrush, tule, flourishes in the marshes. The first accidental cases in man probably occurred during the course of these studies when two members of the expedition contracted an undiagnosed febrile disease, which now appears to have been tularemia, since the following year their blood showed positive agglutination tests.

Following this work deer-fly fever was reported in Utah, the result of the bite of *Chrysops discalis*, and ulcerative conjunctivitis due to the bacterium was reported by Vail and others. In 1914 Werry and Lamb reported infections in man due to *Pasteurella tularensis*, and Werry recorded in 1914 the transmissibility of this disease from rodents to man. In 1919 Francis

isolated *Pasteurella tularensis* from seven patients and seventeen jack-rabbits, and proved that the fly, *Chrysops discalis*, transmitted the disease. He himself and five of his laboratory workers contracted the disease accidentally. In 1923 he further showed that the nonfatal glandular type of "tick-fever" in Idaho was tularemia, and that the wood tick, *Dermacentor andersoni* Stiles, transmits the disease. Indeed, this tick may transmit the germ through its eggs to its offspring. The disease has been shown to be transmitted from rabbit to rabbit by the tick and rabbit-louse, although it is likely that any biting insect may transmit the disease. In rodents the disease is often fatal; large numbers of jack-rabbits, snowshoe rabbits, cottontails, and squirrels often die from its ravages. It has been reported as a disease of rodents and man from coast to coast and in states throughout the country. In rodents the lymph nodes, spleen, and liver contain characteristic necrotic foci, and the organism may be isolated fairly readily.

In man the laboratory tests are especially important and final. Complement fixation tests are positive with *Pasteurella tularensis* as an antigen. However, the most rapid test is that of agglutination. Usually the serum runs a fairly high titer, agglutinins appearing after two weeks and sometimes lasting for years. One must, therefore, be careful in evaluating the agglutination test to see how important past disease must be considered and the present clinical history must support the diagnosis.

There are two clinical types of the disease in man, the glandular and the typhoid. In the glandular or field type the incubation period is from two to nine days, averaging four and a half. The victim may or may not have known that he was bitten by a horsefly or a wood tick. The onset is sudden, with headache, chilly sensations, bodily pains, vomiting, prostration, and fever. The same onset and course maintain in those who have acquired the infection by cleaning rabbits. Within forty-eight hours after the onset there is pain in the glands draining the infected area, which may be the neck, face, conjunctiva, hand, or leg, and the glands are found to be tender and slightly enlarged. Twenty-four hours later the site of the infection becomes a

painful, swollen, inflamed papule, which speedily breaks down, liberating a necrotic core or plug and leaving an ulcer about 0.75 cm. in diameter with raised edges and a punched-out appearance. There are no other physical signs. The fever lasts from two to three weeks and may reach 104° F.; it may be continuous or there may be marked remissions. There is usually a remission on the third or fourth day. The skin over the glands is red and this may be continuous with the site of the infection or there may be red streaks. In half the cases the glands proceed to suppuration and the abscess ruptures through a soft thin spot in the skin. In the others the glands remain hard, palpable, and rather tender for two or three months, gradually returning to normal. There may be delirium. The leukocytes may be moderately increased. Convalescence is slow, the patient usually not getting back to work until the third month, and then only for half-time for another month. There are no complications, although there may be weakness for from six months to a year. Only three deaths have occurred and these not directly from the disease. In the one necropsy performed typical lesions were found in the liver and spleen. The typhoid or laboratory type of tularemia occurs in laboratory workers. There is no local lesion, the infection apparently invading the unbroken skin, although there are no glandular enlargements. The disease runs a course similar to the glandular type.

So far as we are aware there is no specific treatment for tularemia, so that acute cases must be treated along the usual lines that are employed for the treatment of infectious fevers. The most serious part of the illness is the long debilitation in the summer, which keeps the busy farmer, who is most liable to contract the disease, from his labor at the most important time of the year. The convalescence is slow and the prostration marked; fatalities are fortunately rare.

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* Francis prefers the name *Bacterium tularense* to *Pasteurella tularensis* as used in the Bergey Manual.